ORIGINAL SUBMISSION

January 31, 2008

Robert L. Martin
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD
U.S.A. 20740-3835

Re: Revised GRAS Notice for L-Glutathione for Use as a Food Ingredient

Dear Dr. Martin:

As per the recommendations provided by the agency in response to our submission of the GRAS Exemption Claim on December 27, 2007, please accept the enclosed revised notice of a generally recognized as safe (GRAS) exemption claim for the use of L-Glutathione as a food ingredient, in compliance with the GRAS notification procedure described in Federal Register 62 FR 18937, dated April 17, 1997. Enclosed please find four (4) copies of the GRAS Notice, each containing: a signed exemption claim, detailed information on the notified substance, information on any self-limiting levels of use, and a detailed summary of the basis for the GRAS determination.

This notice replaces the original notice submitted on December 27, 2007.

I trust that you will find the enclosed Notice acceptable. Please contact me should you have any questions regarding the submitted notice. I look forward to receiving acknowledgement of receipt of this notice.

Sincerely,

Tetsuo Kato

Encl.

L-Glutathione GRAS Notification

Submitted by:

KOHJIN Co., Ltd
1-21, Nihombashi Muromachi 4 Chome
Chou-ku, Tokyo, 103-0022, JAPAN

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997) (U.S. FDA, 1997)]

L-Glutathione[1], as defined in the report in Appendix I entitled, " **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-GLUTATHIONE FOR USE AS A FOOD INGREDIENT"**, dated November 26, 2007, has been determined by Kohjin Co., Ltd. (KOHJIN) to be Generally Recognized as Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures, as described in the following sections, and on the consensus opinion of an independent panel of experts qualified by scientific training and expertise to evaluate the safety of L-Glutathione under the conditions of its intended use in food. Therefore, the use of L-Glutathione in food as described below is exempt from the requirement of premarket approval.

Signed,

Jan. 30, 2008

Yosuke Uchida
Kohjin Co., Ltd.
1-21, Nihombashi Muromachi 4 Chome
Chou-ku, Tokyo, 103-0022, Japan

Date

B. Name and Address of Notifier

Yosuke Uchida
Kohjin Co., Ltd
1-21, Nihombashi Muromachi 4 Chome
Chou-ku, Tokyo, 103-0022, Japan
yosuke.uchida@kohjin.co.jp

C. Common Name of the Notified Substance

Glutathione

[1] L-Glutathione is the current trade name for KOHJIN's glutathione ingredient; however, a different trade name may be selected in the future.

D. Conditions of Intended Use in Food

KOHJIN intends to market L-Glutathione as a food ingredient in the United States in a variety of food products including baked goods and baking mixes, beverages and beverage bases, breakfast cereals, cheeses, chewing gum, coffee and tea, condiments and relishes, dairy product analogs, fats and oils, gelatins, puddings and fillings, grain products and pastas, gravies and sauces, hard candy, meat products, milk products, plant protein products, processed fruits and fruit juices, processed vegetables and vegetable juices, soft candy, soups and soup mixes, and sugar substitutes [see Appendix I - **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-GLUTATHIONE FOR USE AS A FOOD INGREDIENT**].

As L-Glutathione will be marketed for use in meat products, this Notice also will be reviewed by the United States Department of Agriculture (USDA).

The consumption of L-Glutathione from all proposed food uses was estimated using the proposed food uses and use levels in conjunction with food consumption data included in the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2007). On an all-user basis, the mean intake of L-Glutathione by the total U.S. population from all proposed food uses was estimated to be 340 mg/person/day or 7.92 mg/kg body weight/day. The heavy consumer (90^{th} percentile) all-user intake of L-Glutathione by the total U.S. population from all proposed food uses was estimated to be 690 mg/person/day or 14.93 mg/kg body weight/day.

Consumption of natural cheese and cookies made the most significant contribution to the estimated mean and 90^{th} percentile all-person intakes of L-Glutathione, at 31.5 and 86.58 mg/person/day, respectively (0.55 and 1.56 mg/kg body weight/day, respectively). The consumption of sports and isotonic beverages, instant coffee (powdered), ice teas (powdered), ready-to-eat cereals, hard candy, crackers, chocolate confectionary, processed cheese, and canned soup also contributed significantly to the estimated all-person intakes of L-Glutathione.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, L-Glutathione has been determined by KOHJIN to be GRAS on the basis of scientific procedures (U.S. FDA, 2007a). This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of L-Glutathione as a component of food. The safety of L-Glutathione is supported by its inherent presence in biological systems and important role in detoxification, published toxicological and clinical studies, the results of which indicate no adverse effects relevant to the intended conditions of use of L-Glutathione in foods, and information on the background dietary consumption of glutathione and its metabolic fate [see Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-GLUTATHIONE FOR USE AS A FOOD INGREDIENT**].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Mr. Tetsuo Kato
Kohjin Co., Ltd
1-21, Nihombashi Muromachi 4 Chome
Chou-ku, Tokyo, 103-0022, Japan

Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, KOHJIN will supply these data and information.

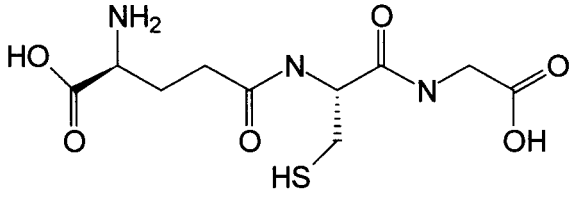
II. Detailed Information About the Identity of the Substance

A. Identity

L-Glutathione is a white crystalline powder that is freely soluble in water, diluted alcohol, liquid ammonia, and dimethylformamide (Merck, 2006).

Common or Usual Name:	Glutathione
Chemical Name:	Glutathione reduced; Glutathione, Reduced Form; 5-L-Glutamyl-L-cysteinylglycine; Glycine, N-(N-L-gamma-glutamyl-L-cysteinyl)-; GSH; L-Glutathione reduced; Reduced glutathione; gamma-L-Glutamyl-L-cysteinylglycine
Chemical Abstracts Service (CAS) Number:	70-18-8
Empirical Formula:	$C_{10}H_{17}N_3O_6S$
Molecular weight:	307.33 g/mol

Structural Formula:



B. Method of Manufacture

L-Glutathione is manufactured *via* a fermentation process using torula yeast, which is permitted for direct addition to food by the U.S. Food and Drug Administration (FDA) (21 CFR 172.896) (U.S. FDA, 2007b). The strain of yeast used in the manufacturing process of L-Glutathione is non-genetically modified torula yeast strain IAM4264. Following fermentation, the yeast culture is washed with water, and the resulting yeast/water suspension is heated to extract L-Glutathione from the yeast by breaking the cell membrane. The glutathione is then separated from the resulting yeast cell mixture using several processes common to the food industry, including centrifugation, complexation, ultrafiltration, ion exchange, washing, and crystallization, resulting in a final product of high purity (>98% GSH).

C. Specifications for Food Grade Material

In order to ensure a consistent product, KOHJIN established numerous specification parameters of the final ingredient (see Table 1), and representative lots of the manufactured product are

routinely analyzed to verify that the manufacturing process produces a consistent product within final product physical, chemical, and microbiological parameters. L-Glutathione is produced in accordance with current Good Manufacturing Practices and meets appropriate food-grade specifications, and all processing aids in the manufacture of L-Glutathione (*i.e.*, components of the fermentation medium, pH adjusting agents, antifoaming agents, and equipment) are appropriate for food use. Furthermore, comprehensive analyses of potential residues from the manufacturing process have confirmed the purity of the final product.

Table 1 Product Specifications for L-Glutathione

Specification Parameter	Specification	Method of Analysis
Appearance	White crystals or crystalline powder	Visual inspection
Glutathione	Not less than 98.0%	JP, Glutathione assay method
Loss on drying	Not more than 0.5%	JP, Loss on drying test
Residue on ignition	Not more than 0.1%	JP, Residue on ignition test
Lead	Not more than 1 ppm	JP, Heavy metals limit test, Method 2
Arsenic	Not more than 1 ppm	JP, Arsenic limit test, Method 1
Total plate count	Not more than 3,000 CFU/g	JFSA (with modification)
Yeast and Mold (CFU)	Not more than 100 CFU/g	JFSA (with modification)
Coliforms	Negative	JFSA (with modification)
Salmonella sp.	Negative	JFSA (with modification)

CFU = colony forming units; JFSA = Japan Food Sanitation Act; JP = Japanese Pharmacopeia
Note: Remainder of components (1.4%) consists of oxidized glutathione (GSSG) and other impurities such as cystenyl-glycine and glutamyl-cysteine.

D. Stability

Stability studies indicated that L-Glutathione is stable when stored in an airtight container at room temperature and normal relative humidity levels for 39 months.

Glutathione is an endogenous tripeptide molecule, comprising the 3 amino acids cysteine, glycine, and glutamate. When dissolved in water and stored under conditions of variable pH for 7 days at room temperature, L-Glutathione is more stable at pH values of 3 to 6 (approximately 80% of the original amount of L-Glutathione remaining in the solution) than at lower or higher values (approximately 65% remaining in the solution at pH 2 and 7). The major degradation products formed at lower pH values are cysteinylglycine (CG) (up to 20% of the original amount of L-Glutathione is degraded to CG) and pyroglutamic acid (PA) (up to 10%), while at higher pH values, L-Glutathione is primarily oxidized (up to 30%, with 5% CG formed as well). When stored at various temperatures for 7 days at a constant pH of 3, L-Glutathione dissolved in water is stable at lower temperatures (more than 85% L-Glutathione remaining at 4 to 25°C, with up to 10% CG formed), but is degraded primarily to CG and PA at higher temperatures. At 60°C, approximately 20% L-Glutathione remains, with 40%, 35%, and 5% of CG, PA, and oxidized

glutathione formed, respectively. Minor degradation products include oxidized CG (occurring at 0.5 to 2%) and glutathione-cysteinylglycine mixed disulfide (occurring at 0.5 to 5%).

Both CG and PA are intermediates formed in the metabolism of reduced glutathione (GSH). GSH is metabolized to CG and gamma-glutamyl-amino acid, the latter of which is converted to PA (also known as 5-oxoproline). PA is subsequently converted to the amino acid glutamate, which is one of the components of GSH. Oxidized glutathione occurs naturally in various foods at levels 2 to 3-fold higher than GSH (Wierzbicka *et al.*, 1989), and there is evidence of a mechanism in the small intestine of rats that reduces oxidized glutathione (Hagen *et al.*, 1990). Oxidized CG, also known as cysteinylglycine disulfide, occurs in the human plasma at higher levels than the reduced form (Mansoor *et al.*, 1992). Although glutathione-cysteinylglycine mixed disulfide has not been measured in humans, it is likely present as mixed disulfides are commonly occurring compounds. Furthermore, if ingested glutathione-cysteinylglycine mixed disulfide were to be reduced, the resulting products would be GSH and CG, which occur endogenously. Therefore, the formation of these products during storage of L-Glutathione in solution at various pH levels and temperature is of no safety concern.

III. Self-Limiting Levels of Use

The use of L-Glutathione in food and beverage products is self-limiting due to its sour taste and sulfur odor.

IV. Basis for GRAS Determination

The determination by KOHJIN that L-Glutathione is GRAS is on the basis of scientific procedures [see Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-GLUTATHIONE FOR USE AS A FOOD INGREDIENT**], which is supported by the views of experts, qualified by scientific training and experience to evaluate the safety of L-Glutathione under the intended conditions of use in food, as specified herein. The safe use of L-Glutathione is based on generally available published scientific information in relation to the intended conditions of use of the ingredient in foods. A summary of this information is provided in Appendix I **[EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-GLUTATHIONE FOR USE AS A FOOD INGREDIENT]**.

V. References

CDC. 2006. Analytical and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES). Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS); Hyattsville, Maryland. Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf.

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Mansoor, M.A.; Svardal, A.M.; Ueland, P.M. 1992. Determination of the in vivo redox status of cysteine, cysteinylglycine, homocysteine, and glutathione in human plasma. Anal Biochem 200(2):218-229.

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U.S. FDA. 2007a. Part 170—Food additives. § 170.30—Eligibility for classification as generally recognized as safe (GRAS). In: U.S. Code of Federal Regulations (CFR). Title 21—Food and Drugs (Food and Drug Administration). U.S. Government Printing Office (GPO); Washington, DC, pp. 13-15. Available from: http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr170.30.pdf.

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USDA. 2007. What We Eat in America: National Health and Nutrition Examination Survey (NHANES): 2003-2004. U.S. Department of Agriculture (USDA); Riverdale, Maryland. Available from: http://www.ars.usda.gov/Services/docs.htm?docid=13793#release.

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Consensus Statement

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF L-GLUTATHIONE FOR USE AS A FOOD INGREDIENT

November 26, 2007

At the request of Kohjin Co., Ltd. (KOHJIN), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened on 14 June 2007 to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use as a food ingredient, L-Glutathione[1], derived from torula yeast, *Candida utilis*, would be Generally Recognized as Safe (GRAS) based on scientific procedures. In the United States (U.S.), torula yeast is a multipurpose additive permitted for direct addition to food for human consumption. The Panel consisted of the below-signed qualified scientific experts: Prof. Jack Bend, Ph.D. (University of Western Ontario), Prof. Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University, Medical College of Virginia), and Prof. Gary M. Williams, M.D. (New York Medical College). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of data provided by KOHJIN. In addition, the Panel evaluated other information deemed appropriate or necessary, including scientific data compiled from the literature and other published sources through March 2007 by Cantox Health Sciences International. The information evaluated by the Panel included data pertaining to the method of manufacture and product specifications of L-Glutathione, supporting analytical data, the intended use levels of L-Glutathione in specified food products, consumption estimates for all intended uses, and a comprehensive assessment of the available scientific literature pertaining to the safety of L-Glutathione.

Following critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use in traditional foods described herein, L-Glutathione derived from torula yeast, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food-grade specifications, is safe and suitable and GRAS based on scientific procedures. The safety of the ingredient is based on the results of published toxicological and clinical studies of reduced glutathione (GSH), as well as its inherent presence in biological systems and important role in cellular defenses, and information on the background

[1] "L-Glutathione" is the trade name of KOHJIN's ingredient, which occurs as the reduced form. L-Glutathione is the current trade name for KOHJIN's ingredient, however, a different trade name may be selected in the future. In this document, "glutathione" refers to reduced and oxidized forms of glutathione, GSH refers to the reduced form, and GSSG refers to the oxidized form.

dietary consumption of glutathione and its metabolic fate. The GRAS status of L-Glutathione is based on this available published scientific information in relation to the intended conditions of use of the ingredient in foods. A summary of the basis for the Panel's conclusion, excluding confidential information, is provided below.

MANUFACTURING, COMPOSITION, AND STABILITY

L-Glutathione is manufactured *via* a fermentation process using torula yeast, which is permitted for direct addition to food by the U.S. Food and Drug Administration (FDA) (21 CFR 172.896) (U.S. FDA, 2007). The strain of yeast used in the manufacturing process of L-Glutathione is non-genetically modified torula yeast strain IAM4264. Following fermentation, the yeast culture is washed with water, and the resulting yeast/water suspension is heated to extract L-Glutathione from the organism by breaking the cell membrane. The glutathione is then separated from the resulting yeast cell mixture using several processes common to the food industry, including centrifugation, complexation, ultrafiltration, ion exchange, washing, and crystallization, resulting in a final product of high purity (>98% GSH).

KOHJIN's L-Glutathione ingredient meets appropriate food-grade specifications and all processing aids used in the manufacture of the ingredient (*i.e.*, components of the fermentation medium, pH adjusting agents, antifoaming agents, and equipment) are appropriate for food use. In order to ensure a consistent product, KOHJIN established numerous specification parameters of the final ingredient (see Table 1), and representative lots of the manufactured product are routinely analyzed to verify that the manufacturing process produces a consistent product within final product physical, chemical, and microbiological parameters. Furthermore, comprehensive analyses of potential residues from the manufacturing process have confirmed the purity of the final product.

Table 1 Product Specifications for L-Glutathione

Specification Parameter	Specification	Method of Analysis
Appearance	White crystals or crystalline powder	Visual inspection
Glutathione (GSH)	Not less than 98 0%	JP, Glutathione assay method
Loss on drying	Not more than 0 5%	JP, Loss on drying test
Residue on ignition	Not more than 0 1%	JP, Residue on ignition test
Lead	Not more than 1 ppm	JP, Heavy metals limit test, Method 2
Arsenic	Not more than 1 ppm	JP, Arsenic limit test, Method 1
Total plate count	Not more than 3,000 CFU/g	JFSA (with modification)
Yeast and Mold (CFU)	Not more than 100 CFU/g	JFSA (with modification)
Coliforms	Negative	JFSA (with modification)
Salmonella sp.	Negative	JFSA (with modification)

CFU = colony forming units; JFSA = Japan Food Sanitation Act; JP = Japanese Pharmacopeia
Note: Remainder of components (1 4%) consists of oxidized glutathione (GSSG) and other impurities such as cysteinyl-glycine and glutamyl-cysteine.

The stability of L-Glutathione was evaluated under various conditions, including high temperature and relative humidity, UV light, day light (lamp), and direct sunlight. The results of these analyses indicated that L-Glutathione is stable when stored in an airtight container at room temperature and normal relative humidity levels for 39 months. L-Glutathione should not be exposed to strong light or high humidity levels.

Glutathione is an endogenous molecular comprising the three amino acids, cysteine, glycine, and glutamate. When dissolved in water and stored under conditions of variable pH for 7 days at room temperature, L-Glutathione is more stable at pH values of 3 to 6 (approximately 80% of the original amount of L-Glutathione remaining in the solution) than at lower or higher values (approximately 65% remaining in the solution at pH 2 and 7). The major degradation products formed at lower pH values are cysteinylglycine (CG) (up to 20% of the original amount of L-Glutathione is degraded to CG) and pyroglutamic acid (PA) (up to 10%), while at higher pH values, L-Glutathione is primarily oxidized (up to 30%, with 5% CG formed as well). When stored at various temperatures for 7 days at a constant pH of 3, L-Glutathione dissolved in water is stable at lower temperatures (more than 85% L-Glutathione remaining at 4 to 25°C, with up to 10% CG formed), but is degraded primarily to CG and PA at higher temperatures. At 60°C, approximately 20% L-Glutathione remains, with 40%, 35%, and 5% CG, PA, and oxidized glutathione formed, respectively. Minor degradation products include oxidized CG (occurring at 0.5 to 2%) and glutathione-cysteinylglycine mixed disulfide (occurring at 0.5 to 5%).

Both CG and PA are intermediates formed in the metabolism of glutathione. GSH is metabolized to CG and gamma-glutamyl-amino acid, the latter of which is converted to PA (also known as 5-oxoproline). PA is subsequently converted to the amino acid glutamate, which is one of the components of GSH. Glutathione disulfide (GSSG), the oxidized form of glutathione, occurs naturally in various foods at levels 2 to 3-fold higher than does GSH (Wierzbicka *et al.*, 1989), and there is evidence of a mechanism in the small intestine of rats that reduces GSSG (Hagen *et al.*, 1990a). Cysteinylglycine disulfide, or oxidized CG, occurs in the human plasma at higher levels than the reduced form (Mansoor *et al.*, 1992). Although glutathione-cysteinylglycine mixed disulfide has not been measured in humans, it is likely present as mixed disulfides are commonly occurring compounds. Furthermore, if ingested glutathione-cysteinylglycine mixed disulfide were to be reduced, the resulting products would be GSH and CG, which occur endogenously. Therefore, the formation of these products during storage of L-Glutathione in solution at various pH levels and temperature is of no safety concern.

INTENDED USE AND ESTIMATED EXPOSURE OF L-GLUTATHIONE

L-Glutathione is intended for use as a food ingredient in the U.S. in a variety of food products, including baked goods and baking mixes, beverages and beverage mixes, breakfast cereals, cheeses, chewing gum, instant coffee, condiments, dairy product analogs, fats and oils, gelatins, puddings, and fillings, grain products and pastas, sauces, hard and soft candy, meat,

milk, and plant protein products, processed juices, soups and soup mixes, and sugar substitutes. The proposed food uses and use-levels are provided in Table 2.

Table 2 Summary of the Individual Proposed Food Uses and Use Levels for L-Glutathione in the United States*

Food Category	Proposed Food Use	Use Level (mg/Serving)	RACC** (g or mL)	Maximum Use Level (%)
Baked Goods and Baking Mixes	Cookies	100	30 or 40	0 333
	Crackers	100	30	0 333
Beverages and Beverage Bases	Ice Teas (Powdered)	300	15	2 000
	Sports and Isotonic Beverages	300	240	0 125
Breakfast Cereals	Instant and Regular Hot Cereals	50	40 or 55	0.125
	Ready-to-Eat Cereals	50	15 or 55	0 333
Cheeses	Cottage Cheese	50	110	0.045
	Cream Cheese	50	30	0 167
	Imitation Cheese	50	30	0 167
	Natural Cheese	50	30	0 167
	Processed Cheese	50	30	0 167
Chewing Gum	Chewing Gum	200	3	6 667
Coffee and Tea	Instant Coffee (Powdered)	100	15	0.667
Condiments and Relishes	Soy Sauce	10	15	0 067
	Vinegar	10	15	0 067
Dairy Product Analogs	Hypo-Allergenic Infant Formulas	200	120	0 167
	Soy-Based Meal Replacements (Powdered)	100	15	0 667
	Soy Milk	50	240	0.021
Fats and Oils	Margarine	10	15	0 067
	Vegetable Oils (Includes Salad Dressings)	10	15 or 30	0 067
Gelatins, Puddings, and Fillings	Gelatin, Jams, and Jelly	50	15 or 120	0 333
	Gelatin Drinks	100	240	0.042
	Puddings	30	120	0.025
Grain Products and Pastas	Gratin	30	30	0.100
	Pizza (Crust)	30	140	0 021
	Ready-Made Noodles and Canned Pasta	30	245	0 012
Gravies and Sauces	Barbecue Sauces	10	30	0 033
	Gravy Sauces	10	60	0 017
Hard Candy	Hard Candy	300	15	2.000
	Mints	100	2	5 000

Table 2 Summary of the Individual Proposed Food Uses and Use Levels for L-Glutathione in the United States*

Food Category	Proposed Food Use	Use Level (mg/Serving)	RACC** (g or mL)	Maximum Use Level (%)
Meat Products	Ham (Processed and Cured)	50	55	0 091
	Meat Sauces	30	125	0 024
	Sausages (Includes Dried)	50	30 or 55	0 167
	Stews	30	240	0.013
Milk Products	Cocoa Powder Mixtures	10	15	0.067
	Milk-Based Meal Replacements (Powdered)	100	15	0.667
	Milk (Dry and Powdered Mixtures)	100	15	0 667
	Yoghurt (Includes Frozen)	200	120 or 225	0.167
	Yoghurt Drinks	200	240	0 083
Plant Protein Products	Plant-Protein-Based Meal Replacements (Powdered)	100	15	0.667
	Protein Bars	100	40	0.250
Processed Fruits and Fruit Juices	Fruit Flavored Drinks (Powdered)	100	15	0 667
Processed Vegetables and Vegetable Juices	Vegetable Juices	100	240	0 042
Soft Candy	Chocolate Confectionary	100	40	0.250
	Soft Candy	100	40	0.250
Soups and Soup Mixes	Canned Soups	100	245	0.041
	Consommé	10	245	0 004
	Dehydrated and Powdered Soup Mixes	100	30	0.333
Sugar Substitutes	Sugar Substitutes	5	4	0 125

* The proposed food uses and use levels for L-Glutathione in the United States also include milk- and soy-based infant formulae, and these categories were evaluated under the scope of this GRAS determination, however, as this is a future marketing venture for KOHJIN and will require an additional regulatory submission to the FDA, these food uses have not been included in this table with the other proposed food uses

** RACC = Reference Amounts Customarily Consumed per Eating Occasion [21 CFR §101.12 (U S. FDA, 2007)]. When a range of values is reported for a proposed food-use, particular foods within that food-use may differ with respect to their RACC.

As L-Glutathione will be marketed for use in meat products, the data and information provided in this document will be reviewed by the U.S. Department of Agriculture (USDA). As a future venture, KOHJIN intends to market L-Glutathione for use in milk- and soy-based infant formulae at a level of up to 200 mg/serving or a maximum use level, based on Reference Amounts Customarily Consumed per Eating Occasion (RACC) [21 CFR § 101.12 (U.S. FDA, 2007)], of 0.167%. Pursuant to the *Federal Food, Drug, and Cosmetic Act* (FFDCA), KOHJIN recognizes that persons responsible for the manufacture or distribution of infant formula must register the formulation with the FDA and make a submission to the FDA for any new infant formula (or any

infant formula that has had a major change in its formulation or processing) at least 90 days before any charitable or commercial distribution. Additionally, after the first processing of a new infant formula, but before marketing, persons responsible for the manufacture or distribution of the infant formula must submit to the FDA a written verification which demonstrates that the formula, as actually produced, complies with the requirements of the FFDCA. Therefore, although the safety of adding glutathione to infant formulae is being assessed as a component of this GRAS determination, L-Glutathione will not be marketed in the U.S. for use in infant formulas until it has met the requirements relating to infant formula as described in the FFDCA.

Estimates for all-person and all-user intakes of L-Glutathione for specific demographic groups and for the total U.S. population were calculated based on the proposed food-uses and use-levels in conjunction with food consumption data included in the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2007). Approximately 99.4% of the total U.S. population was identified as consumers of L-Glutathione from the proposed food-uses (8,213 actual users identified). On an all-user basis, the mean intake of L-Glutathione by the total U.S. population from all proposed food-uses was estimated to be approximately 340 mg/person/day or 7.92 mg/kg body weight/day (see Table 3). The heavy consumer (90^{th} percentile) all-user intake of L-Glutathione by the total U.S. population from all proposed food-uses was estimated to be 694 mg/person/ day or 14.93 mg/kg body weight/day (see Table 4). Infants were determined to have the highest mean all-user intake of L-Glutathione of 521.19 mg/person/day (61.10 mg/kg body weight/day) and the highest 90^{th} percentile all-user intake of L-Glutathione of 1,468.26 mg/person/day (194.19 mg/kg body weight/day); however, it should be noted that L-Glutathione will not be marketed for use in infant formulae until approval has been granted by the FDA, and hence the estimated highest intakes for the remaining population groups will be considered. On an absolute basis, the greatest mean and 90^{th} percentile all-user intakes of L-Glutathione were estimated to occur in male teenagers, at 410.14 and 808.95 mg/day, respectively. On a body weight basis, the greatest mean and 90^{th} percentile all-user intakes of L-Glutathione were highest in children, with intakes of 13.03 and 26.56 mg/kg body weight/day, respectively (see Table 4).

Table 3	Summary of the Estimated Daily Intake of L-Glutathione from All Proposed Food Categories in the U.S. by Population Group (2003-2004 NHANES Data)						
Population Group	**Age Group (Years)**	**% Users**	**Actual # of Total Users**	**All-Person Consumption**		**All-User Consumption**	
				Mean (mg)	**90th Percentile (mg)**	**Mean (mg)**	**90th Percentile (mg)**
Infants*	0 to 2	95.2	885	502 87	1,451.16	521 19	1,468.26
Children	3 to 11	100 0	1,287	348 41	623 96	348.41	623.96
Female Teenagers	12 to 19	99.6	988	292.68	568 04	293.75	568.04
Male Teenagers	12 to 19	99.8	997	409.70	808.33	410 14	808 95
Female Adults	20 and Up	100.0	2,128	288 85	572 72	289.08	572.72
Male Adults	20 and Up	99.9	1,928	365 44	742 73	365.45	742 73
Total Population	All Ages	99 4	8,213	339 22	693 38	339.94	694 17

• Includes estimated intake from proposed uses in milk- and soy-based infant formulae.

Table 4	Summary of the Estimated Daily per Kilogram Body Weight Intake of L-Glutathione from All Proposed Food Categories in the U.S. by Population Group (2003-2004 NHANES Data)						
Population Group	**Age Group (Years)**	**% Users**	**Actual # of Total Users**	**All-Person Consumption**		**All-User Consumption**	
				Mean (mg/kg bw)	**90th Percentile (mg/kg bw)**	**Mean (mg/kg bw)**	**90th Percentile (mg/kg bw)**
Infants*	0 to 2	95.2	885	58 95	191 01	61.10	194.19
Children	3 to 11	100.0	1,287	13.03	26.56	13 03	26 56
Female Teenagers	12 to 19	99 6	988	5.13	10.94	5.15	10 94
Male Teenagers	12 to 19	99 8	997	6 55	13.82	6.56	13 83
Female Adults	20 and Up	100 0	2,128	4 15	8 53	4.15	8.53
Male Adults	20 and Up	99.9	1,928	4 32	8.73	4 32	8 73
Total Population	All Ages	99 4	8,213	7 90	14 89	7 92	14 93

* Includes estimated intake from proposed uses in milk- and soy-based infant formulae.

Consumption of natural cheese and cookies made the most significant contribution to the estimated mean and 90th percentile all-person intakes of L-Glutathione, at 31.5 and 86.58 mg/person/day, respectively (0.55 and 1.56 mg/kg body weight/day, respectively). The consumption of sports and isotonic beverages, instant coffee (powdered), ice teas (powdered), ready-to-eat cereals, hard candy, crackers, chocolate confectionary, processed cheese, and canned soup also contributed significantly to the estimated all-person intakes of L-Glutathione.

DATA SUPPORTING THE SAFETY OF L-GLUTATHIONE

The safety of L-Glutathione is based the results of published toxicological and clinical studies of GSH, information on the background dietary consumption of GSH and its subsequent metabolic fate, as well as its presence endogenously in humans. Acute, chronic, and developmental toxicity studies have been conducted on glutathione in animals. There also are several clinical trials that have been conducted and published in peer-reviewed scientific journals. Because only a few toxicological studies and clinical trials that included measurements of safety endpoints were identified, several efficacy studies in which no adverse effects attributable to GSH treatment were reviewed as support for the safety of L-Glutathione.

Endogenous Presence of Glutathione

GSH is synthesized endogenously from the amino acids L-cysteine, L-glutamate, and glycine *via* γ-glutamylcysteine synthetase. The liver is the major site for the production and export of GSH, although virtually all cell types have the capacity to synthesize GSH.

Knowledge regarding the daily synthesis of GSH is limited due to complex compartmentalization of substrates and their metabolism at both the subcellular and organ levels (Wu *et al.*, 2004). Furthermore, GSH synthesis is affected by numerous factors, including oxidative stress and insult (Griffith, 1999). Lyons *et al.* (2000) reported the mean absolute synthesis rate of GSH in healthy adult males as 748 µmol/L/day in whole blood. Assuming a blood volume of 5 L for the average adult, this value is equivalent to 1.15 g GSH/day. According to the authors, whole blood GSH synthesis may account for approximately 10% of whole body synthesis; therefore, it is estimated that 11.5 g GSH is synthesized in the body on a daily basis.

Glutathione occurs ubiquitously in human tissues, predominantly in its reduced form (GSH). Reported GSH levels in whole blood range from 684 to 2,525 µmol/L, which would be equivalent to total blood amounts of approximately 1 to 4 g[2] (Pastore *et al.*, 2003). GSH is present in animal cells at levels of 0.5 to 10 mmol/L (Wu *et al.*, 2004). Extracellular GSH content is orders of magnitude lower, with typical plasma levels of 5 to 50 µmol/L (Griffith, 1999). In neonatal infants, glutathione content in erythrocytes was reported in several studies, with levels of approximately 7 to 9 µmol/g hemoglobin (Jean-Baptiste and Rudolph, 2003; Lee and Chou, 2005), corresponding to 0.08 to 0.13 g total glutathione in the blood[3] (primarily GSH with a small fraction as GSSG).

Although GSH levels in the gut lumen of humans have not been measured, luminal GSH levels in the gastrointestinal tract of fasting rats range from 6 µM in the stomach to 0.5 mM in the

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[2] These values were calculated based on the assumption that the human body contains 5 L of blood. Sample calculation: 684 µmol/L x 307.33 g/mol x 5 L blood = ~1 g GSH

[3] These values were calculated based on the assumption that the concentration of hemoglobin (Hb) in the blood is 150 g/L and that the neonatal body contains 0.25 to 0.32 L of blood (70 to 90 ml/kg body weight x 3.5 kg body weight). Sample calculation: 7 µmol/g Hb x150 g Hb/L blood x 307 33 g/mol x 0.25 L blood = ~0.08 g total glutathione.

duodenum (Hagen *et al.*, 1990a), indicating that even in the absence of a dietary source, GSH is present in the small intestine. It also was demonstrated that GSH in the duodenum is derived from the bile. The authors suggested that luminal GSH may serve to detoxify xenobiotics present in the bile or food or may be absorbed for participation in intracellular detoxification reactions.

GSH is oxidized non-enzymatically to GSSG by reaction with electrophilic substances, including reactive oxygen/nitrogen species and free radicals. Under normal conditions, GSH levels are maintained by GSH reductase; however, GSSG may accumulate under conditions of oxidative stress, and may be secreted from the cell and degraded extracellularly contributing to a net loss of intracellular GSH levels. Because of the high concentration gradient between intracellular and extracellular GSH, influx of GSH or GSSG back into cells is thermodynamically unfavorable; however, exogenous GSH can be useful for increasing plasma and tissue GSH concentrations as, depending on the tissue, orally administered GSH may increase tissue GSH concentrations directly *via* uptake of intact GSH by transporters (as observed in the rat jejunum, lung and brain), indirectly through degradation of GSH and subsequent intracellular re-synthesis (liver), or by a combination of both mechanisms (heart) (Favilli *et al.*, 1997).

Natural Occurrence and Background Dietary Intake

GSH was reported to occur at a level of 5 to 20 mg/100 g in fresh meats, fish, and poultry (mean 9.7 mg/100 g), and at 4 to 15 mg/100 g in fruits (mean 3.2 mg/100 g) and vegetables (mean 4.7 mg/100 g) (Wierzbicka *et al.*, 1989; Jones *et al.*, 1992). GSH content is generally low in breads, cereals, legumes and nuts, oils and fats, sweets and snacks, and beverages (excluding fruit and dairy beverages). Fresh foods contain higher levels of GSH compared to frozen, canned, and processed foods, and cooking tends to decrease the natural GSH content of foods (Wierzbicka *et al.,* 1989; Jones *et al.,* 1992). GSH also has been identified in breast milk (Ankrah *et al.*, 2000).

Glutathione is present in foods, generally in the reduced form (GSH), which is the form that is absorbed in the small intestine (Hagen and Jones, 1989), but also in some foods in all oxidized or disulfide forms, including GSSG (Wierzbicka *et al.*, 1989; Jones *et al.*, 1992), with small amounts available for absorption by the small intestine (Hagen *et al.,* 1990a). Furthermore, it appears that the small intestine possesses a reductive mechanism that reduces GSSG to GSH (Hagen *et al.*, 1990a), potentially resulting in the utilization of GSSG in food.

Estimates of dietary GSH intake may vary substantially due to differences in GSH content among foods and variations in consumption frequency; however, Wierzbicka *et al.* (1989) reported that the estimated dietary intake of GSH in the American population ranges from 2.9 to 131 mg/day, and Flagg *et al.* (1994) estimated daily intake levels of 13 to 110 mg/day. Additionally, in its purified form, GSH is currently sold by a number of manufacturers as a dietary ingredient in supplement products and is commonly manufactured *via* fermentation of

yeast, similar to KOHJIN's L-Glutathione. As a nutritional supplement, GSH is usually supplied in capsule, powder, or tablet form in doses ranging from 50 to 600 mg daily (PDRHealth, 2006).

Metabolic Fate of Oral GSH

The results of studies involving oral administration of GSH to laboratory animals indicated that GSH is absorbed from the gastrointestinal tract intact, and following transport across the epithelial cell, is released into the blood and is taken up by various organs and tissues as needed. Specifically, the administration of GSH by gavage or *via* the diet increased plasma and tissue (*i.e.*, jejunum, lung, heart, liver, and brain) GSH concentrations in rats, but administration of the amino acid constituents of GSH did not affect plasma GSH concentrations, indicating that the increase in GSH concentration resulted from absorption of intact GSH and not from its metabolism and re-synthesis (Hagen *et al.*, 1990b; Favilli *et al.*, 1997). In mice, gavage administration of GSH increased plasma but not tissue GSH concentrations, demonstrating that changes in plasma GSH concentrations did not affect tissue levels and that cellular GSH homeostasis was tightly controlled under GSH-sufficient conditions (Aw *et al.*, 1991). Pre-treatment with a GSH synthesis inhibitor produced decreased tissue GSH levels in the rat, and subsequent oral GSH administration significantly increased GSH levels in all tissues measured (*i.e.*, the kidney, heart, brain, small intestine, and skin) except the liver, likely because this organ does not take up exogenous GSH (Hahn *et al.*, 1978). The principal site of GSH absorption in the rat is the upper jejunum (Hagen *et al.*, 1990a), which contains a sodium-dependent uptake system (Linder *et al.*, 1984; Hunjan and Evered, 1985; Hagen and Jones, 1987; Vincenzini *et al.*, 1987). Circulating GSH is primarily cleared by the kidney (Hahn *et al.*, 1978).

The effects of oral GSH administration on plasma GSH levels in humans also were investigated, with results indicating a similar profile in humans as in laboratory animals. Witschi *et al.* (1992) provided 0.15 mmol GSH/kg body weight (approximately 2.7 g GSH in a 60 kg individual) dissolved in water to 7 healthy male and female volunteers and reported no significant increases in plasma GSH levels when measured at 30 minute intervals for up to 270 minutes, although a transient increase was observed in 2 women and a slight (less than 2-fold) elevation was reported for the 4-hour time-point in 1 man. The authors suggested that the interspecies differences in plasma GSH levels following oral administration may be attributed to higher hepatic gamma-glutamyltransferase (γ-GT) activity in humans compared to rats, resulting in increased hydrolysis of GSH. Metabolism by intestinal γ-GT also may have contributed to the lack of increase in circulating GSH levels in humans. Alternatively, Hagen and Jones (1989) reported an increase in plasma GSH levels in 4 of 5 subjects provided 15 mg GSH/kg body weight orally (0.9 g in a 60 kg individual). Plasma GSH concentrations peaked at 1 hour after administration to 300% of basal levels, and decreased to approximately 200% of baseline values by 3 hours post-GSH ingestion. Administration of the constituent amino acids of GSH to humans did not result in the same increase in plasma GSH as did administration of GSH, demonstrating that GSH is absorbed intact.

Toxicological Studies Using GSH

Due to the paucity of identified oral toxicity studies of GSH, studies involving intravenous administration were included in the safety assessment to support the safety of GSH. Intravenous administration results in 100% bioavailability, providing greater bioavailability of GSH compared to that achieved by oral administration, and therefore, provide a conservative margin of safety when translating to the safety of GSH from oral exposure. A tabular summary of the identified acute and short-term toxicity studies, subchronic and chronic toxicity studies, and carcinogenicity studies is presented in Attachment 2.

Acute and Short-Term Studies

In an acute toxicity study, male ICR-JCL mice, aged 7 to 8 weeks, were administered single doses of GSH sodium *via* oral, intravenous, or subcutaneous administration and were observed for 7 days, and the median lethal dose (LD_{50}) values were reported to be >10,000 mg/kg body weight (oral and subcutaneous) and >5,000 mg/kg body weight (intravenous), which were the highest doses tested (Nozaki *et al.*, 1972).

The efficacy of short-term oral GSH administration (up to 24 hours) for the treatment of toxicity caused by exposure to acetaminophen, methylmercury, and 95% O_2 has been investigated in several studies in laboratory animals (Ogawa *et al.*, 1972; Viña *et al.*, 1989; Brown *et al.*, 1996; Sugimura and Yamamoto, 1998). No adverse effects due to GSH administration were reported in these studies, and GSH was shown to be efficacious in the management of these toxicities.

Subchronic and Chronic Toxicity Studies

In an attempt to define the potential protective effects of oral GSH on the toxicity of inhaled sulfur dioxide (SO_2), mice (dd strain; 3 groups of 10 mice/group or 2 groups of 15 mice/group) and rats (hybrid; 3 groups of 5 rats/group) were administered a diet containing 0.5% TATHION® (a GSH drug product containing 0.1% GSH), providing approximately 150 and 50 mg GSH/kg body weight/day for mice and rats, respectively (U.S. FDA, 1993), while housed in an inhalation chamber providing air with up to 0.4 ppm SO_2 for 6 weeks or 3 months (Oshima and Imai, 1970). The authors reported that the mice exposed to the TATHION® diet and SO_2 had increased body weights in comparison to the mice that did not consume the TATHION® diet. These results were not observed in rats. Furthermore, the number of mice and rats who died during the experimental period was decreased in the animals administered the TATHION® diet. Upon histopathological examination of the lungs, heart, liver, spleen, and kidneys using hematoxylin and eosin staining techniques, there were no differences observed in the mice fed the different diets, but the rats fed TATHION® did not have as severe tissue damage as the rats that were not administered the TATHION® diet. The authors concluded that TATHION® had a positive effect on SO_2-induced toxicity.

Beagle dogs (number not reported) were given a single intravenous dose of 500 or 1,000 mg/kg body weight of GSH sodium (in a saline solution) as a preliminary phase of the chronic toxicity study (no control group was reported). Dogs injected with 500 mg/kg body weight vomited and were less active, and dogs given 1,000 mg/kg body weight exhibited vomiting, salivation, cramping in the 4 extremities and ataxia for approximately 1 hour. Consequently, 300 mg/kg body weight was selected as the maximum daily dose for the chronic study. Six dogs (3 males and 3 females) per treatment group were intravenously administered 0 (control), 30, 100, or 300 mg/kg body weight of GSH sodium per day for 26 weeks. General symptoms and food consumption were measured every day. Body weight was measured once every 2 weeks. Blood samples were taken at 3 time points before administration and at 3, 5, 10, 15, 20, and 25 weeks for measurement of hematology and clinical chemistry parameters. A bromosulfonphthalein and phenolsulfonphthalein excretion test was conducted at 5, 15, and 25 weeks before daily GSH administration. The day after the last injection, the animals were anesthetized and exsanguinated for autopsy. Organ weights were recorded and tissues were stained and subjected to microscopic examination. The results obtained from this study were not reported to be statistically analyzed (Suzuki *et al.*, 1972).

No signs of toxicity were observed at levels of up to 100 mg/kg body weight/day; however, 4 of 6 dogs in the 300 mg/kg body weight/day group vomited several times during the treatment period. Serum glutamic oxaloacetic acid transaminase (GOT) was elevated compared to baseline values and the control animals in 1 male in the 30 mg/kg body weight/day dose group at 25 weeks and 1 male in the 300 mg/kg body weight/day dose group at 20 weeks. The authors concluded that the elevation of GOT was coincidental as only 2 dogs displayed the elevated levels throughout the study. The ovary weights of 1 to 2 females in each of the control, 100, and 300 mg/kg body weight/day dose groups were reported to be heavier than the others in the groups. The authors reported that this was due to the formation of luteal bodies on the ovaries and as the incidence was similar in the control and treatment groups, was considered not to be related to GSH administration. The authors reported that no other abnormalities in the parameters tested were associated with GSH administration. No adverse effects were reported at the highest dose tested in the study (300 mg/kg body weight/day), and therefore, this dose could be considered to be the no observed adverse effect level (NOAEL).

Genotoxicity and Mutagenicity Studies of GSH

The potential mutagenic activity of GSH was assessed in an Ames assay using *Salmonella typhimurium* (*S. typhimurium*) strains TA100, TA1537, TA1538, TA98 and TA1535 (Glatt *et al.*, 1983). No mutagenic activity was reported in any of the bacterial strains tested in the presence or absence of a metabolic activating system [post-mitochondrial supernatant (S9) fraction from the liver or kidney of male Sprague-Dawley rats]; however, significant increases in the number of revertants were observed in TA100 when 5, 10, or 20 mM GSH was incubated with kidney S9. The authors noted that the concentrations of GSH used in this study were similar to

intracellular GSH levels in mammals. GSH also was mutagenic to *S. typhimurium* TA100 when incubated with kidney microsomal fraction but not cytosol.

To investigate the mechanism of *in vitro* GSH mutagenicity in *S. typhimurium* TA100, Ross *et al.* (1986) incubated GSH with various subcellular fractions from the kidneys of male Sprague-Dawley rats, including the post-microsomal supernatant, S9, microsomes, and partially-purified plasma membrane. The highest number of revertants was reported in cells incubated with the kidney plasma membrane fraction, which is rich in the enzymes γ-GT and glutathione oxidase. Incubation with inhibitors of these enzymes (anthglutin to inhibit γ-GT and various metal-chelating agents to inhibit glutathione oxidase) completely inhibited the mutagenic activity of GSH with the plasma membrane fraction and inhibited to varying degrees the mutagenicity of GSH with the S9 fraction. The authors concluded that the mechanism of GSH mutagenicity when incubated with kidney subcellular fractions involved the cleavage of GSH to cysteinyl glycine catalyzed by γ-GT and the activity of free transition metals or enzymes that are dependent on transition metals for their activity, such as glutathione oxidase. The authors also hypothesized that the *in vitro* mutagenic activity of GSH is unlikely to occur *in vivo* because γ-GT and glutathione oxidase are located on the outer surface of kidney cell membranes and are not exposed to high levels of GSH (since the majority of GSH is present intracellularly), and because levels of free metals are tightly controlled by metal-binding proteins.

Carcinogenicity Studies

No traditional carcinogenicity studies of GSH were identified in the literature. A number of studies were identified that involved investigation of the potential of GSH supplementation for cancer prevention and therapy with beneficial results (Novi, 1981; Wagner *et al.*, 1985; Trickler *et al.*, 1993; Schwartz and Shklar, 1996). Neal and Legg (1983) reported that oral (gavage) treatment with 100 mg GSH/day for 10 weeks did not result in the development of lesions in liver sections of male Fischer 344 rats.

Developmental Toxicity Studies

GSH has been tested in developmental toxicity studies conducted in mice and rabbits (Suzuki *et al.*, 1972). In the mouse study, more than 20 pregnant ICR-RLC mice/treatment group (exact number not reported) were administered GSH sodium saline solution intravenously in doses providing 0 (control), 30, 300, or 1,000 mg/kg body weight/day of GSH from gestational days (GD) 7 to 13, and were sacrificed on GD 18. In the second developmental toxicity experiment, pregnant New Zealand white rabbits (more than 8 animals/treatment group, exact number not reported) were given GSH sodium saline solution intravenously in doses providing 0 (control), 80, or 300 mg/kg body weight/day of GSH from GD 8 to 15, and were sacrificed on GD 30 (Suzuki *et al.*, 1972). The rabbits were exsanguinated on day 30 of gestation.

In both studies, general condition, body weight, autopsy findings, and organ weights were normal in the dams of all test groups. The numbers of implantations and dead fetuses, mean

body weight of fetuses, and incidences of external anomalies and skeletal variations in the offspring were similar among all groups. Because no adverse effects were reported at the highest doses tested in the studies (1,000 mg/kg body weight/day in mice and 300 mg/kg body weight/day in rabbits), these doses could be considered to be the NOAEL. The value in the rabbit study supports the NOAEL determined in the dog chronic toxicity study.

Clinical Trials

Details of various clinical studies in patients treated for drug poisoning, auto-intoxication, and pesticide and metal poisoning were provided in a monograph of TATHION® prepared by Yamanouchi Pharmaceutical Co., Ltd. (KOHJIN, personal communication, 2007). Additionally, details of the use of glutathione for treating gestational toxicosis were included in the monograph, although the original study article was not identified. Of the 6,522 patients included in these clinical trials, of which 1,750 patients were provided the ingredient orally, side effects were reported for 24 patients (~0.4%), and included anorexia, nausea and vomiting, without any observed changes in clinical laboratory test values.

Several published studies designed to determine the effects of GSH therapy in the treatment of cancer (Dalhoff *et al.*, 1992), male infertility (Lenzi *et al.*, 1992, 1993), diabetes (Paolisso *et al.*, 1992), and lead poisoning (Nakao *et al.*, 1968) were identified; however, oral administration was utilized in only one of the studies (Dalhoff *et al.*, 1992). In this study, 8 hepatocellular carcinoma patients were given 5,000 mg GSH (dissolved in orange juice) daily beginning shortly after diagnosis. Two patients withdrew from the study because of intolerable side effects, including gastrointestinal irritation and sulfur odor. Of the 6 remaining patients, 5 died within a year of diagnosis of pre-existing hepatocellular carcinoma, but tumors regressed or stabilized in 2 of these patients. The tumor did not progress in the surviving patient.

Murao *et al.* (1974) investigated the efficacy of TATHION® in treating hyperemesis (severe morning sickness) during pregnancy. Subjects between the first day of the 5th week of pregnancy and the sixth day of the 16th week of pregnancy diagnosed with mild (113 patients), moderate (150 patients), or advanced (81 patients) hyperemesis were administered 3 tablets of TATHION® containing 100 mg GSH/tablet or placebo twice daily between meals for 14 days. Symptoms were evaluated during the first consultation and at 1 and 2 weeks after treatment commencement. Blood samples were collected before and after the treatment period for measurement of blood total protein, albumin/globulin ratio, total bilirubin, aspartate aminotransferase, alanine aminotransferase, zinc sulfate turbidity test, alkaline phosphatase, total cholesterol, ketone bodies, red and white blood cells, and urine samples were collected during the same visits for assessment of urinary occult blood, ketone bodies, sugar protein, pH, and urobilinogen. Blood pressure also was measured at these visits. A follow-up survey was conducted to determine if abnormalities occurred in neonates. TATHION® treatment resulted in improvement of major hyperemesis symptoms in moderate cases compared to placebo. No differences in blood and urinalysis measurements between TATHION® and placebo groups were reported. Adverse reactions attributable to TATHION® were not reported, but the authors

stated that it was not possible to distinguish compound-related adverse reactions from hyperemesis symptoms, as they are similar. Results from neonatal follow-up were not reported by the authors.

Kudo (1972) reported the results of 5 subjects diagnosed with organophosphorus pesticide (Parathion) poisoning who were orally administered 300 mg GSH/day for 4 weeks. Treatment with GSH, an endogenous cellular detoxicant, improved serum cholinesterase activity. No adverse event or tolerance reporting were included in the published article.

Summary

GSH is an abundantly-occurring endogenous tripeptide in humans and animal species that serves an important cellular protective function. It is present in all cells, with levels in human blood of approximately 1 to 4 g. Additionally, GSH is present naturally in many foods, including fresh meat products and fruits and vegetables, with the reported dietary intake of GSH ranging from 3 to 130 mg/day. Following oral administration, GSH is absorbed intact, resulting in increased plasma and tissue levels.

KOHJIN's L-Glutathione is produced from a non-genetically-modified strain of torula yeast, which is approved for use in food in the U.S. Extensive purification processes during manufacturing remove the yeast and other processing aids, ensuring that the final product is uncontaminated, with a purity greater than 98%. L-Glutathione is intended for use in a variety of food products, including baked goods and mixes, beverages and mixes, breakfast cereals, cheeses, chewing gum, instant coffee, dairy product analogs, fats and oils, condiments, sauces, gelatins, puddings, and fillings, grain products and pastas, hard and soft candy, meat, milk, and plant protein products, processed juices, soups and soup mixes, and sugar substitutes. The estimated mean and 90th percentile intakes of L-Glutathione from the proposed food-uses are approximately 340 and 694 mg/person/day, respectively.

The published and unpublished data and information evaluated and summarized in this report demonstrate that the proposed uses of L-Glutathione, manufactured consistent with cGMP and meeting appropriate food-grade specifications, are safe and suitable and GRAS under the conditions of use described herein. The safety of the proposed uses of L-Glutathione is based on the inherent nature of glutathione in the diet and in biological systems and on the available published toxicological and clinical studies.

CONCLUSION

We, the Expert Panel, have independently and collectively critically evaluated the data and information summarized above and conclude that the proposed uses of L-Glutathione derived from Torula yeast, *Candida utilis*, manufactured consistent with cGMP and meeting appropriate food-grade specifications, presented above are safe.

We further conclude that the proposed uses are Generally Recognized as Safe (GRAS) based on scientific procedures.

It is our opinion that other qualified experts would concur with these conclusions.

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University of Western Ontario

Dec. 4, 2007
Date

Prof. Joseph F. Borzelleca, Ph.D.
Virginia Commonwealth University, Medical College of Virginia

29 November 2007
Date

Prof. Gary M. Williams, M.D.
New York Medical College

30 November 2007
Date

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Lenzi, A.; Culasso, F.; Gandini, L.; Lombardo, F.; Dondero, F. 1993. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod 8(10):1657-1662.

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Wagner, G.; Frenzel, H.; Wefers, H.; Sies, H. 1985. Lack of effect of long-term glutathione administration on aflatoxin B1-induced hepatoma in male rats. Chem Biol Interact 53(1&2):57-68.

Wierzbicka, G.T.; Hagen, T.M.; Jones, D.P. 1989. Glutathione in Food. J Food Comp Anal 2(4):327-337.

Witschi, A.; Reddy, S.; Stofer, B.; Lauterburg, B.H. 1992. The systemic availability of oral glutathione. Eur J Clin Pharmacol 43(6):667-669.

Wu, G.; Fang, Y.Z.; Yang, S.; Lupton, J.R.; Turner, N.D. 2004. Glutathione metabolism and its implications for health. J Nutr 134(3):489-492.

Attachment 1

Attachment 1

Curriculum Vitae of Expert Panel Members

CURRICULUM VITAE
GARY MURRAY WILLIAMS, M.D.

EDUCATION:	Washington and Jefferson College, Washington, Pa. B.A. 1963; Magna Cum Laude
	University of Pittsburgh School of Medicine, Pittsburgh, Pa. M.D., 1967

SUBSEQUENT TRAINING AND POSITIONS;

1967-1969	Intern and Resident in Pathology, Department of Pathology, Massachusetts General Hospital and Instructor in Pathology, Harvard University Medical School, Boston, Massachusetts.
1969-1971	Staff Associate, National Cancer Institute, Experimental Pathology Branch, Chemical Carcinogen Screening Unit, Bethesda, Maryland.
1971-1972	Visiting Scientist, Wenner-Gren Institute, Department of Cell Physiology, Stockholm, Sweden.
1971-1975	Assistant Professor, Department of Pathology, and Member, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania.
1975-1979	Research Associate Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1979-1999	Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1999 - present	Professor of Pathology, Department of Pathology, Director of Environmental Pathology and Toxicology, Head, Program on Medicine, Food and Chemical Safety, New York Medical College, Valhalla, New York; Professor of Clinical Public Health, School of Public Health, New York Medical College, Valhalla, New York.

CERTIFICATIONS:

1974	American Board of Pathology
1975	Physician, State Education Department, State of New York
1981	American Board of Toxicology, Recertified, 2002.
1984	Expert in Toxicology, Ministere des Affaires Sociales et de la Solidarite Nationale, Direction de la pharmacie et du medicament, Republic Francais
2000	Fellow in Toxicologic Pathology, International Academy of Toxicologic Pathology
2002	Fellow of the Royal College of Pathologists

AWARDS AND HONORS:

1963	Phi Beta Kappa, Washington and Jefferson College
1967	Sheard-Sandford Award, American Society of Clinical Pathologists
1967	Alpha Omega Alpha, University of Pittsburgh School of Medicine
1971	Research Training Fellowship, International Agency for Research on Cancer
1980	Association of University Pathologists
1980	Invited Contributor, Special Issue Food and Cosmetics Toxicology, 9:557, 1981, dedicated to Leon Golberg
1982	Arnold J. Lehman Award, Society of Toxicology
1984	Invited Contributor, Hommage au Professeur Rene Truhaut
1987	Citation Classics: Cancer Lett. 1:231, 1976 and Cancer Res. 37:1845, 1977. Institute for Scientific Information, Current Contents, Vol. 30, No.36, September 7, 1987

1988	Citation Classics: In Vitro 12:521, 1976; 12:821, 1976; 13:809, 1977, 14:824, 1978. Institute for Scientific Information. Current Contents, Vol. 32, No. 9, February 27, 1989
1989	Featured on cover of Cancer Research, Volume 49, November 1
1995	Featured on cover of Cancer Research, Volume 55, April 15
1996	Awards Lecture, Society of Toxicology
1997	Invited Contributor, Special Issue Cancer Letters, 118:1, 1997, dedicated to Phillipe Shubik
1997	Top 10 Most Frequently Cited Articles in 25 years of Toxicologic Pathology Toxicologic Pathology 10:3-10, 1982; Toxicologic Pathology 26:452, 1998
2001	Ambassador in Toxicology Award, Mid-Atlantic Chapter of the Society of Toxicology.
2002	Enhancement of Animal Welfare Award, Society of Toxicology.
2005	American Chemical Society, New York Section, Inc. Westchester Chemical Society Distinguished Scientist Award – 2005.
2006	New York Medical College Dean's Distinguished Research Award, 2005.
2006	Food and Agriculture Organization / World Health Organization Joint Expert Committee on Food Additives. 50th Anniversary Medal (5 years service.)

RECOGNITION:

1996-06	Who's Who in America (1995-2006) 50th-60th Editions
1996-06	Who's Who in the East (1995-2006) 26-33rd Editions
1996-06	Who's Who in Science and Engineering (1995-2006) 3rd-8th Editions
2005-06	Who's Who in American Education (2006-07) 6th-7th Editions
2005-06	Who's Who in Medicine and Healthcare (2006-07) 5th-6th Editions
1997/1998	American Men and Women of Science Directory of American Research & Technology

1998-05	Official American Board of Medical Specialties Directory of Board Certified Medical Specialists 30th-38th Editions

SOCIETIES:

1974	American Association for Cancer Research
1978	Society of Toxicology
1981	Society of Toxicologic Pathologists
1991	International Society of Regulatory Toxicology and Pharmacology

EDITORIAL RESPONSIBILITIES:

1980	Co-Editor, Differentiation and Carcinogenesis in Liver Cell Cultures. Vol. 349. New York Academy of Sciences.
1980-1981	Consulting Reviewer, Oncology Overviews, International Cancer Research Data Bank.
1980-1986	Reviewing Editor, In Vitro.
1980	Co-editor, The Predictive Value of In Vitro Short-term Screening Tests in Carcinogenicity Evaluation. Elsevier/North Holland Biomedical Press.
1981-1983	Editorial Board, Fundamental and Applied Toxicology.
1981-1989	Editorial Board, Toxicology and Applied Pharmacology.
1981-1999	Editorial Board, Nutrition and Cancer.
1981	Meeting Report: Carcinogenesis and Gene Expression in Liver Cultures. Cancer Research 42:2462-2464, 1982.
1982	Consulting Reviewer, Oncology Overview, International Cancer Research Data Bank Program, National Cancer Institute.
1982-1993	Editorial Board, Mutation Research, Genetic Toxicology Testing Section.
1983	Co-Editor, Colon Carcinogenesis. CRC Press.
1983	Co-Editor, Cellular Systems for Toxicity Testing. Vol. 407. New York Academy of Sciences.

1983	Co-Editor, Tests Courts de Cancerogenese/Short-term Tests for Carcinogenesis, Elsevier Science Publishers BV, Amsterdam.
1983-1992	Editorial Board, Chemico-Biological Interactions.
1983-1996	Editorial Board, Toxicologic Pathology.
1984-present	Founding Editor, Cell Biology and Toxicology.
1987	Meeting Report: Causative and Modifying Factors in Digestive Tract Cancer. Cancer Research 47:922-923, 1987
1988-present	Editorial Board, Archives of Toxicology
1987	Editor, Sweeteners: Health Effects, Princeton Scientific Publishing Company.
1988	Editorial Board, Complex Mixtures and Cancer Risk, IARC Scientific Publications, International Agency for Research on Cancer
1989	Meeting Report: American Health Foundation 20th Anniversary International Symposium on Causes and Prevention of Cancer. Preventive Medicine, in 20:534-547, 1991
1991-present	International Advisory Board, European Journal of Cancer Prevention
1992	Proceedings of the Second International Conference on Longevity and Aging: Environmental and Nutritional Influences on Aging and Cancer Experimental Gerontology, Volume 27, Special Issue, 1992
1993	Editor-in-Chief, Antioxidants Chemical, Physiological, Nutritional and Toxicological Aspects, Princeton Scientific Publish. Co.
1994-present	Area Editor for Carcinogenesis, Drug and Chemical Toxicology.
1997	Co-Editor, Reducing Dietary Fat: Putting Theory into Practice, Journal of The American Dietetic Association, Volume 97, Supplement 1, 1997
2001	Co-Editor, Toxicology, Special Issue, Volume 166, Number 3, Festschrift J.H. Weisburger.

2002	Guest Editor, International Symposium on Antimutagenesis and Anticarcinogenesis, European Journal of Cancer Prevention, Volume 11, Supplement 2.
2003	Editorial Board, Toxicologic Pathology.
2005	International Editorial Board, Food and Chemical Toxicology.

MEETINGS ORGANIZED:

1980	Conference on Differentiation and Carcinogenesis in Liver Cell Cultures. New York Academy of Sciences. New York, NY.
1980	Workshop on the Predictive Value of in vitro Short Term Screening Tests in the Evaluation of Carcinogenicity. Scientific Council of the Netherlands Cancer Society. Dalen, The Netherlands.
1982	Quo Vadis Symposium on Short Term Tests in Carcinogenesis and Mutagenesis. Research Center Clin-Midy. Montpellier, France.
1983	Conference on Carcinogenesis and Gene Expression in Liver Cultures United States-Japan Cooperative Cancer Research Program. Honolulu, Hawaii.
1984	Conference on Cellular Systems for Toxicity Testing, New York Academy of Sciences, New York, NY.
1986	Conference on Causative and Modulating Factors for Digestive Tract Cancer United States-Japan Cooperative Cancer Research Program. Tokyo, Japan.
1986	International Conference on Cancer Research. Theories of Carcinogenesis. The Norwegian Cancer Society, Oslo, Norway.
1986	Conference on Non-Mutagenic Carcinogens: How Much Risk to Man? The Robens Institute, University of Surrey, Guildford, England.
1987	Conference on Sweeteners: Health Effects. American Health Foundation, New York.
1987	International Symposium in Genetic Toxicology, National Science Foundation (U.S.) and Council of Scientific and Industrial Research (India), University of Calcutta, Calcutta, India.

1988	International Symposium on Causes and Prevention of Cancer, American Health Foundation in cooperation with American Cancer Society and National Cancer Institute, New York, NY.
1989	International Conference on Environmental and Nutritional Influences on Aging and Cancer, American Health Foundation in cooperation with National Institute on Aging, New York, NY.
1990	Conference on Cancer Prevention for Black Americans, Metropolitan Life Insurance, Company, New York, NY.
1991	International Conference on Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects, American Health Foundation, Tarrytown, NY.
1991	Second International Conference on Theories of Carcinogenesis. Norwegian Cancer Society, Oslo, Norway.
1992	1st International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.
1993	2nd International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.
1993	American Health Foundation, 25th Anniversary Conference and Celebration, Toward Optimal Health: Examining Goals for Nutrition and the Environment, Tarrytown, NY.
1994	3rd International Course on the Safety Assessment of Pharmaceuticals, Tarrytown, NY.
1995	International Congress on Hepatocytes-Applications in Cell Biology, Toxicology and Medicine, Tubingen, Germany.
1996	Conference, Reducing Dietary Fat: Putting Theory Into Practice, American Health Foundation, New York, NY.
1996	4th International Course on the Safety Assessment of Pharmaceuticals, Part I, White Plains, NY.
1996	4th International Course on the Safety Assessment of Pharmaceuticals, Part II, San Francisco, CA.

1997	5th International Course on the Safety Assessment of Medicines, Part I, White Plains, NY.
1998	6th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2000	7th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2001	8th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2002	International Symposium on Antimutagenesis and Anticarcinogenesis, New York Medical College, Valhalla, NY
2002	10th International Course on the Safety Assessment of Medicines, Advanced Course, Hyéres, Var, France.
2002	International Symposium on Agricultural Exposures and Cancer, Oxford, England.
2003	Symposium, Chemical Safety Assessment: Contribution of Toxicological Pathology and Mechanistic Investigations, New York Medical College, Valhalla, NY.
2004	11th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2005	12th International Course on the Safety Assessment of Medicine Basic and Regulatory Aspects, White Plains, NY.
2006	Symposium "Current Issues in Safety Assessment of Medicines, NYMC Valhalla, NY.
2006	13th International Course on the Safety Assessment of Medicines, White Plains, NY.

NATIONAL AND INTERNATIONAL RESPONSIBILITIES

1975	Consultant, Pesticides, Toxic Substance and Solid Waste Management, United States Environmental Protection Agency.

1975-1978	Member, Epidemiology Committee, Breast Cancer Task Force, NationalCancer Institute.
1976-1977	Member, Program Committee, American Association for Cancer Research.
1976	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man: Some Miscellaneous Pharmaceutical Substances, International Agency for Research on Cancer.
1976-1978	Co-Chairperson, Subcommittee on Rat Liver Tumors, Committee on Histologic Classification of Laboratory Animal Tumors, Institute of Laboratory Animal Resources, National Research Council.
1977-1978	Member, Panel on Kepone/Mirex, Scientific and Technical Assessments of Environmental Pollutants, Environmental Studies Board, Commission on Natural Resources, National Research Council.
1979-1980	Member, Panel on Unscheduled DNA Synthesis, Gene-Tox Program, U.S. Environmental Protection Agency.
1980-1981	Member, Panel of Experts Associated with Technical Report Review Subcommittee, National Toxicology Program, Department of Health and Human Services.
1980	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man-Antineoplastic and Immunosuppressive Drugs, International Agency for Research on Cancer.
1980-1986	Panel of Reviewers, Netherlands Cancer Foundation.
1981	Advisor, Technical Committee, Society of Toxicology.
1981-1982	Member, Task Group on the Differentiation Between Genotoxic and Epigenetic Carcinogens, International Commission on Protection Against Environmental Mutagens and Carcinogens.
1982	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemicals and Industrial Processes Associated with Cancer in Humans, IARC Monographs Volumes 1 to 29, International Agency for Research on Cancer.
1982-1983	Consultant, Office of Health and Environmental Assessment, Reproductive Effects Assessment Group, U.S. Environmental Protection Agency.

1982-1983	Member, International Expert Committee to the Nutrition Foundation on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, Nutrition Foundation, Incorporated.
1982-1983	Coordinator, Assays of DNA Damage, Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity. International Programme on Chemical Safety, World Health Organization.
1983	Member, Working Group on the Mechanisms of Chemical Carcinogenesis, International Agency for Research on Cancer.
1983-1984	Member, Expert Committee on Pathology/Toxicology and Expert Committee on Short-Term Testing, International Life Sciences Institute.
1984-1987	Assessor, National Health and Medical Research Council Panel of Independent Assessors, National Health and Medical Research Council, Commonwealth of Australia.
1984-1985	Member, Committee on the Carcinogenicity of Cyclamates, Food and Nutrition Board, Commission on Life Sciences, National Research Council.
1984-1985	Member, Task Group of DNA Repair, Subcommittee on Genetic Toxicology, American Society for Testing and Materials.
1985-1987	Member, Toxicology Study Section, National Institutes of Health.
1985	Vice-Chairman, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Naturally Occurring Substances, Food Additives and Amino Acid Pyrolysates in Food, International Agency for Research on Cancer.
1985-1986	Member, Awards Committee, Society of Toxicology.
1986	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, International Agency for Research on Cancer.
1987	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, International Agency for Research on Cancer.
1988	Participant, Tox-90s Conference, Society of Toxicology.

1989	Organizing Committee, Workshop on the Effects of Pesticides on Human Health, Task Force on Environmental Cancer and Heart and Lung Disease.
1989	Chairman, Working Group and Chairman, Subgroup on Animal Carcinogenicity, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Humans: Some Pharmaceutical Drugs, International Agency for Research on Cancer.
1989	Participant and Member of Editorial Board, Workshop on Complex Mixtures and Cancer Risk, International Agency for Research and Cancer.
1989	Participant, Working Group on Short-Term In Vitro and In Vivo Tests, Workshop on Research to Improve Predictions of Long-Term Chemical Toxicity, National Research Council.
1990-present	Member, Committee of Education on Toxicologic Pathology, International Federation of Societies of Toxicologic Pathologists.
1991	Member, Working Group on Approaches to Classifying Carcinogens According to Mechanisms of Action, International Agency for Research on Cancer.
1993-1999	Member, Committee on Evaluation of the Research Program "Cancer Risk Factors and Prevention," German Cancer Center.
1993-2005	Member, Board of Trustees, International Life Sciences Institute, Health and Environmental Sciences Institute. Chair, Membership Development Committee, 2002-2003.
1993-present	Member, Subcommittee on Carcinogenicity, International Federation of Societies of Toxicologic Pathologists.
1995-1996	Consultant, International Life Sciences Institute, North America Antioxidant Technical Committee.
1995-1997	Member, Committee on Research Opportunities and Priorities for EPA, Commission on Geosciences, Environment, and Resources, National Research Council.
1996	Reviewer, U.S. Environmental Protection Agency (EPA), PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures.

1996	Participant, Developmental Planning for Office of Dietary Supplements (ODS), National Institutes of Health.
1997	Member, Working Group on Short/Medium Term Carcinogenicity Tests and Genetic and Related Effects. International Agency for Research on Cancer.
1998	Member, Working Group - Re-evaluation of Some Industrial Chemicals. International Agency for Research on Cancer.
1999-2003	Member, Subcommittee on Upper Safe Reference Levels of Nutrients, Committee on Reference Levels of Nutrients, National Academy of Sciences, Institute of Medicine.
1999	Member, Working Group on Predictive Value of Gastric Neuroendocrine Tumours and Forestomach Tumours in Rodents for Carcinogenic Hazard Identification. Co-Chairperson, Forestomach Tumors. International Agency for Research on Cancer.
2000	Member and Report Coordinator, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel. U.S. Environmental Protection Agency.
2000-2004	Reviewer, Office of Dietary Supplements, National Institutes of Health. Annual Bibliography of Significant Advances in Dietary Supplement Research.
2001-present	Member, Accreditation Committee, International Academy of Toxicologic Pathology.
2002	Peer Review Member, U.S. Environmental Protection Agency "Perchlorate Environmental Contamination: Toxicological Review and Risk Assessment."
2002	Temporary Advisor, World Health Organization, 59th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO.
2002	Participant, Joint FAO/WHO Project to Update the Principles and Methods or the Risk Assessment of Chemicals in Food. Workshop I: Introduction, Toxicological Tests & Evaluation, Human Data, Margins of Safety.
2003	Panelist, Dietary Supplement Use in the Elderly Conference. Office of Dietary Supplements. National Institutes of Health.

2003	Temporary Member, Metabolic Pathology Study Section, National Institutes of Health.
2003-2005	Member, Workgroup on Mechanism of Action in Assessing Human Relevance of Animal Tumors, Risk Science Institute, International Life Science Institute.
2003	Temporary Advisor, World Health Organization, 61st Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA).
2004	Temporary Advisor, World Health Organization, 63rd Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA).
2004 -05	Member WHO Task Group on Environmental Health Criteria for Modelling Dose-Response for the Risk Assessment of Chemicals, World Health Organization.
2004	Temporary Advisor, World Health Organization International Programme on Chemical Safety Author's Workshop on Dose-Response Modeling, World Health Organization.
2004-06	Member, Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds. National Research Council, National Academies of Science.
2005	Member, International PPAR Task Force, International Atherosclerosis Society.
2005	Temporary Advisor, World Health Organization, 65th Meeting of the Joint Food and Agriculture Organization / World Health Organization Expert Committee on Food Additives (JECFA).
2005	International Life Sciences Institute, Health and Environmental Sciences Institute, Emerging Issues Subcommittee on Biological Significance of DNA Adducts.
2006	International Life Sciences Institute, Health and Environmental Sciences Institute, Scientific Advisor.
2006	Institute of Life Sciences Europe Expert Group on the Application of the Margin of Exposure (MOE) Approach to Genotoxic Carcinogens in Food.

2006 Temporary Advisor, World Health Organization, 67th Meeting of the Joint Food and Agriculture Organization / World Health Organization Expert Committee on Food Additives (JECFA).

BIBLIOGRAPHY 1969-2006

490 publications

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Joseph Francis Borzelleca

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Educational Background:

B.S. St. Joseph's University, Philadelphia, PA, Major: Biology, Chemistry.

M.S. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, Major: Pharmacology, Physiology.

Ph.D. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA. Major: Pharmacology, Biochemistry.

Academic Appointments

Instructor-Associate: Department of Pharmacology, Medical College of Pennsylvania, 1956-1959.

Assistant Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1959-62 and 1962-1967.

Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1967-

Head: Division of Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, 1972-1986.

Professor Emeritus: Pharmacology & Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, July 1996 –

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **

American Association for the Advancement of Science

American Chemical Society

American College of Toxicology*

American Society of Pharmacology and Experimental Therapeutics**

(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)

International Society of Regulatory Toxicology and Pharmacology*

(Member of Council)

Sigma XI

Society of Experimental Biology and Medicine*

(Councilor; Program Chairman of Southeastern Section)

Society for Risk Analysis

Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)

Virginia Academy of Science*

(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI

Board of Scientific and Policy Advisors

American Council on Science and Health

Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board

Environmental Carcinogenesis Reviews, 1981-

Journal of Environmental Pathology, Toxicology and Oncology 1977-

Journal of Environmental Science and Health, 1979-

Journal of the American College of Toxicology, 1982-

Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992

Journal of Applied Toxicology, 1989-

Pharmacology, 1978-

Pharmacology and Drug Development, 1980-

Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

Food and Drug Administration

National Institute of Mental Health

National Cancer Institute

Environmental Protection Agency

Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)

U.S. Army - Research and Development Command

Non-Governmental

National Academy of Sciences - NRC

Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards

Safe Drinking Water Committee

Evaluation of Household Substances Committee (1138 Committee)

Food Protection Committee

Food Additives Survey Committee

Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes

Committee on Risk Assessment of Flame-Retardant Chemicals

Federation of American Societies of Experimental Biology

Select Committee on GRAS Substances

Flavors and Extracts

Biotechnology Product Safety

Caprenin GRAS Committee

World Health Organization

Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)

NATO/CCMS Drinking Water Committee

Industrial

Chemical Companies; Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (11960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)

Planning and participation in continuing education program
(Schools of Dentistry, Medicine and Pharmacy)

Planning and administering each of the three major efforts in pharmacology

(dental, medical, pharmacy) since 1960.

Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Presents lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

Elected senator from the graduate school, then vice-president of the University Senate
Served on various committees (e.g. Curriculum, Search, Animal Care) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

Research

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S.; N.I.H; E.P.A.; N.I.D.A.) and non-governmental (industrial). A list of publications is attached).

Awards

DOD - US Army - Chemical Research Development and Engineering Center

Distinguished Service Award, 1986

National Italian - American Foundation Award

Excellence in Medicine and Community Service, 1987

Thomas Jefferson University

Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences

Outstanding Faculty Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences, Dept. of Pharmacology and Toxicology

Professor of the Year- 1992

American College of Toxicology

Distinguished Service Award- 1997

Virginia's Life Achievement in Science Award- April 2001

2001 Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists

PUBLICATIONS

Borzelleca, J.F. and Manthei, R.W.: Factors influencing pentobarbital sleeping time in mice. Arch. Int. Pharmacodyn. 111:296, 1957.

Borzelleca, J.F.: Studies of the contribution of bladder absorption to the physiological changes induced by pentobarbital. J. Pharm. Exp. Ther 129:305, 1960.

Borzelleca, J.F.: The absorption of nicotine from the urinary bladder of the dog. Arch. Int. Pharmacodyn. 133:444, 1961.

Borzelleca, J.F., Bowman, E.R. and McKennis, H., Jr.: The cardiovascular and respiratory effects of (-)-cotinine. J. Pharmacol. Exp. Ther. 137:313,1962.

Borzelleca, J.F.: Drug absorption from the urinary tract of the rat. Nicotine. Arch. Int. Pharmacodyn. 143:595,1963.

Borzelleca, J.F.: Influence of saline and glucose infusions on the course of barbiturate intoxication. Arch. Int. Pharmacodyn. 146: 163, 1963.

Larson, P.S., Borzelleca, J.F., Bowman, E.R., Crawford, E.M., Smith, R.B., Jr. and Henningar, G.R.: Toxicologic studies on a preparation of p-tertiary octylphenoxy-polyethoxy ethanols (Trition X-405). Toxicol. Appl. Pharmacol. 5:782, 1963.

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Borzelleca, J.F. and Doyle, C.H.: Excretion of drugs in saliva. Salicylate, barbiturate, sulfanilamide. J. Oral. Therap. Pharmacol. 3:104, 1966.

Borzelleca, J.F. and Lowenthal, W.: Drug absorption from the rectum. II. J. Pharm. Sci. 55:151, 1966.

Wooles, W.R. and Borzelleca, J.F.: Prolongation of barbiturate sleeping time in mice by stimulation of the reticuloendothelial system. J. Reticuloendo. Soc. 3:41, 1966.

Wooles, W.R., Borzelleca, J.F. and Branham, G.W.: The effects of acute and prolonged salicylate administration on liver and plasma triglyceride levels and dietary-induced hypercholesterolernia. Toxicol. Appl. Pharmacol. 10:1. 1967.

Borzelleca, J.F., Harris, T. and Bernstein, S.: The effect of DIVISO on drug movement through the wall of the urinary bladder of the rabbit. J. Invest. Urol. 6:43, 1968.

Borzelleca, J.F.: The excretion of glucose in saliva. Dog. J. Oral Therap. Pharmacol. 4:338, 1968.

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Borzelleca, J.F. and Putney, J.W., Jr.: Studies on the biotransformation of salicylic acid by the salivary gland. Arch. Int. Pharmacodyn. 188:127, 1970.

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Munson, A.E., Barrett, B.A. and Borzelleca, J. F.: *In vitro* experimental approaches to detection of sensitive agents. In: Cutaneous Toxicity, (V. Drill, ed.), Academic Press, Inc., San Francisco, p. 175, 1977.

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Carmines, E.L., Carchman, R.A. and Borzelleca, J.F.: Kepone: Cellular sites of action. Toxicol. Appl. Pharmacol. 49:543, 1979.

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Larson, P.S., Egle, J.L., Jr., Hennigar, G.R. and Borzelleca, J.F.: Acute and subchronic toxicity of mirex in the rat, dog, and rabbit. Toxicol. Appl. Pharmacol. 49:271, 1979.

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Weiner, M.L., Steinberg, M., Borzelleca, J.F., Enters, EX, Hager, D.F., Kinoshita, F.K., Loper, A., Mitchell, D.B. and Tamulinas, C.B.: Proposed safety evaluation guidelines for new excipients. Toxicologist 13:213 (#796), 1994

Borzelleca, J.F.: The safety evaluation of macronutrient substitutes. IFT Annual Meeting Abstracts #15-2, 1994

Borzelleca, J.F.: Fat replacers. ACS meeting, 1995

Rice, R.G., Graham, D.M., Glaze, W.H., Pariza, M.W., Newell, G.W., Erdman, J.W., and Borzelleca, J.F.: Ozone preservation of Foods and Foodstuffs. 13th Ozone World Congress, October 1997, Kyoto, Japan

Lien, E., Boyle, F., Perry, Thompson, C., Borzelleca, J.F., and Wrenn, J.: Comparison of AIN-76A and AIN-93G Diets in Rats; a 13 Week Study. Fed. Proc., 1998

Munro, E.C., Berndt, W.O., Borzelleca, J.F., Flamm, G., Lynch, B.S., Kennepohl, E., Bar, A. and Modderman, J.: Erythritol: An Interpretive Summary of Biochemical, Metabolic, Toxicological and Clinical Data. Toxicologist 38: 1999

BOOKS and BOOK CHAPTERS

Skalsky, H.L., Lane, R.W. and Borzelleca, J.F.: "Excretion of carbaryl into saliva of the rat and its effect on cholinesterase". In: Toxicology and Occupational Medicine (W.B. Deichman, ed.), p. 349, 1979.

Borzelleca, J.F. and Carmines, E.L.: "New drug evaluation: safety assessment". In: Program for Applied Research on Fertility Regulation, 1980.

Hayes, J.F. and Borzelleca, J.F.: "Biodisposition of environmental chemicals by animals". In: Animal Products in Human Nutrition (D. Beitz and R. Hansen, eds.), Chap. 11, p. 225. Academic Press, New York, 1982.

Borzelleca, J.F.: "Neurobehavior toxicological testing". Pharmacodependence and neurobehavioral toxicology. Quo Vadis ?, Symposium "Quo Vadis ?", Sanofi Group, Montpellier, France, p. 115, 1983.

Schwartz, S.L. and BorzelleGa, J.F.: "Toxicology of polyvinylpyrrolidone". Proceedings of the International Symposium on Povidone (G.A. Digenis,Ed.), College of Pharmacy, University of Kentucky, Lexington, KY, p. 234,1983.

Borzelleca, J.F., Hallagan, J. and Reese, C. "Food, Drug and Cosmetic Colors: Toxicological Considerations." ACS Symposium Series, No. 234, Xenobiotics in Foods and Feeds. (Finley, J.W. and Schwass, D.E., eds.), Chap. 20, p.31 1. ACS, Washington, D.C., 1983

Borzelleca, J.F.: "Extrapolation of animal data to man". In: Toxicology Laboratory Design and Management for the 80's and Beyond (Tegeris, A.S., Ed); Vol. 1 of Concepts in Toxicology, Homburger, F., Series Ed.), 1984.

Borzelleca, J.F.: "Current concepts in reproductive toxicology". In: Clinics in Laboratory Medicine, Symposium on Environmental and Occupational Health Hazards, Vol. 4 (R.V. Blanke, ed.), W.B. Saunders Co., Philadelphia, 1984.

Borzelleca, J.F., Condie, L.W., and Hayes, J.R.: "Toxicological evaluation of selected chlorinated phenols". In Water Chlorination, Chemistry, Environmental Impact and Health Effects. (R.L. Jolley, R.J. Bull, W.P. Davis, S. Katz, M.H. Roberts, Jr., V.A. Jacobs). Volume 5, Chap. 26, p.331. Lewis Publishers, Inc., Ann Arbor, Michigan, 1985.

Robinson, B.V., Sullivan, F.M., Borzelleca, J.F. and Schwartz, S.L.: PVP: A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone). Lewis Publishers, Inc., Ann Arbor, Michigan. 1990

Borzelleca, J.F. and Hallagan, J.B.: "Safety and Regulatory Status of Food, Drug, and Cosmetic Colors." ACS Symposium Series, No. 484, Food Safety Assessment. (Finley, J.W., Robinson, S.F., and Armstrong, D.J., eds.), Chap. 31, p.377. ACS, Washington, DC. 1992

Borzelleca, J.F. "Foods of the Future: What Will We Be Eating in the Next Century?" In Practical Handbook of Nutrition in Clinical Practice (Kirby, D.F. and Dudrick, S.J., eds.), Chap. 16, p.279. CRC Press, Inc., Boca Raton, Fl. 1994

Borzelleca, J.F.: "History of Toxicology." In Principles and Methods of Toxicology (Hayes, A.W., editor), edition 3, Chap. 1, p 1-18, Raven Press, New York, NY. 1994

Matt, D.W. and Borzelleca, J.F.: "Toxic Effects on the Female Reproductive System During Pregnancy, Parturition, and Lactation." In Reproductive Toxicology (Witorsch, R.J., editor), edition 2, chapter 10, p. 175 Raven Press, New York, NY. 1995

Borzelleca, J.F.: "Food-Borne Health Risks: Food Additives, Pesticides and Microbes." In Nutrition Policy in Public Health (Bronner, F., editor). Chap. 3, p.33, Springer Publishing Co. New York, NY. 1997

Rice, R.G., Graham, D.M., Glaze, W.H., Pariza, M.W., Newell, G.W., Erdman, J.W., and Borzelleca, J.F.: Ozone Preservation of Foods and Foodstuffs. 13th Ozone World Congress, Kyoto, Japan, October 1997

Borzelleca, J.F. and Weiner, M.L. : "Development of Safety Evaluation Guidelines." In Excipient Toxicity and Safety (Weiner, M. L. and Kotkoskie, L. A., editors). Chapter 5, p.101. Marcel Dekker, Inc., New York, N.Y. 1999

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Research Office, Federation of American Societies of Experimental Biology (FASEB):

Evaluation of the health aspects of iron and iron salts as food ingredients. 1973.

Evaluation of the health aspects of butylated hydroxytoluene as a food ingredient. 1973.

Evaluation of the health aspects of certain zinc salts as food ingredients. 1973.

Evaluation of the health aspect of pulps as they may migrate to food from packaging materials. 1973.

Evaluation of the health aspects of propylene glycol and propylene glycol monostearate as food ingredients. 1973.

Evaluation of the health aspects of alginates as food ingredients. 1973.

Evaluation of the health aspects of agar-agar as a food ingredient. 1973.

Evaluation of the health aspects of certain red and brown algae as food ingredients. 1973.

Evaluation of the health aspects of cellulose and certain cellulose derivatives of food ingredients. 1973.

Iodine in foods: chemical methodology and sources of iodine in the human diet. 1974.

Evaluation of the health aspects of aconitic acid as a food ingredient. 1974.

Evaluation of the health aspects of stannous chloride as a food ingredient. 1974.

Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycrrhizin as food ingredients. 1974.

Evaluation of the health aspects of Gaprylic acid as a food ingredient. 1974.

Evaluation of the health aspects of sorbose as a food ingredient. 1974.

Evaluation of the health aspects of sulfuric acid and sulfates as food ingredients. 1974.

Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients. 1975.

Evaluation of the health aspects of dextran as food ingredients. 1975.

Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients. 1975.

Evaluation of the health aspects of succinic acid as a food ingredient. 1975.

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of certain calcium salts as food ingredients. 1975.

Evaluation of the health aspects of glycerin and glycerides as food ingredients 1975

Evaluation of the health aspects of dextrin and corn dextrin as food ingredients. 1975.

Evaluation of the health aspects of sodium thiosulfate as a food ingredient. 1975.

Evaluation of the health aspects of gelatin as a food ingredient. 1975.

Evaluation of the health aspects of bile salts and ox bile extract as food ingredients. 1975.

Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients. 1975.

Evaluation of the health aspects of aluminum compounds as food ingredients. 1975.

Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients. 1975.

Evaluation of the health aspects of phosphates as food ingredients. 1975.

Evaluation of the health aspects of the tocopherols and a-tocopheryl acetate as food ingredients. 1975.

Evaluation of the health aspects of sorbic acid and its salts as food ingredients. 1975.

Evaluation of the health aspects of hydrogenated fish oil as a food ingredient. 1975.

Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. 1975.

Evaluation of the health aspects of inositol as a food ingredient. 1975.

Evaluation of the health aspects of malic acid as a food ingredient. 1975.

Evaluation of the health aspects of Japan Wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging. 1976.

Evaluation of the health aspects of carnauba wax as a food ingredient. 1976.

Evaluation of the health aspects of sulfamic acid as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of hydrosulfites as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of gum guaiac as a food ingredient. 1976.

Contributing authorship on the following publications of the Life Science Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of corn sugar (dextrose), corn syrup and invert sugar as food ingredients. 1976.

Evaluation of the health aspects of sucrose as a food ingredient. 1976.

Evaluation of the health aspects of sulfiting agents as food ingredients. 1976.

Evaluation of the health aspects of glycerophosphates as food ingredients. 1976.

Evaluation of the health aspects of magnesium salts as food ingredients. 1976. Evaluation of the health aspects of sodium hydroxide and potassium hydroxide as food ingredients. 1976.

Evaluation of the health aspects of adipic acid as a food ingredient. 1976.

Evaluation of the health aspects of hydrogenated soybean oil as a food ingredient.

Evaluation of the health aspects of formic acid, sodium formate, and ethyl formate as food ingredients. 1976.

Evaluation of the health aspects of lard and lard oil as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of pyridoxine and pyridoxine hydrochloride as food ingredients. 1977.

Evaluation of the health aspects of papain as a food ingredient. 1977.

Evaluation of the health aspects of hypophosphites as food ingredients. 1977.

Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they migrate to food from packaging materials, and linoleic acid as a food ingredient. 1977.

Evaluation of the health aspects of pectin and pectinates as food ingredients. 1977.

Evaluation of the health aspects of tannic acid as a food ingredient. 1977.

Evaluation of the health aspects of rennet as a food ingredient. 1977.

Evaluation of the health aspects of acetic acid and sodium acetate as food ingredients. 1977.

Evaluation of the health aspects of sodium oleate and sodium palmitate as substances migrating to food from paper and paperboard used in food packaging. 1977.

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of corn silk as a food ingredient. 1977.

Evaluation of the health aspects of bentonite and clay (kaolin) as food ingredients. 1977

Evaluation of the health aspects of citric acid, sodium citrate, potassium citrate, calcium citrate, ammonium citrate, triethyl citrate, isopropyl citrate, and stearyl citrate as food ingredients. 1977.

Evaluation of the health aspects of lactic acid and calcium lactate as food ingredients. 1978.

Evaluation of the health aspects of calcium pantothenate, sodium pantothenate, and D-pantothenyl acohol as food ingredients. 1978.

Evaluation of the health aspects of Vitamin B12 as a food ingredient. 1978.

Evaluation of the health aspects of Vitamin D2 and Vitamin D3 as food ingredients. 1978.

Evaluation of the health aspects of caffeine as a food ingredient. 1978.

Evaluation of the health aspects of certain glutamates as food ingredients. 1978.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1978.

Evaluation of the health aspects of butylated hydroxyanisole as a food ingredient. 1978.

Evaluation of the health aspects of sodium, potassium, magnesium and zinc gluconates as food ingredients. 1978.

Evaluation of the health aspects of urea as a food ingredient. 1978.

Evaluation of the health aspects of thiamin hydrochloride and thiamin mononitrate as food ingredients. 1978.

Evaluation of the health aspects of biotin as a food ingredient. 1978.

Evaluation of the health aspects of ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. 1979.

Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients. 1979.

Evaluation of the health aspects of casein, sodium Gaseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of soy protein isolates as food ingredients. 1979.

Evaluation of the health aspects of carotene (B-carotene) as a food ingredient. 1979.

Evaluation of the health aspects of nitrogen, helium, propane, n-butane, isobutane, and nitrous oxide as gases used in foods. 1979.

Evaluation of the health aspects of hydrogen peroxide as a food ingredient. 1979.

Evaluation of the health aspects of riboflavin and riboflavin-5-1-phosphate as food ingredients. 1979.

Evaluation of the health aspects of starch and modified starches as food ingredients. 1979.

Evaluation of the health aspects of carbon dioxide as a food ingredient. 1979.

Evaluation of the health aspects of sodium chloride and potassium chloride as food ingredients. 1979.

Evaluation of the health aspects of certain silicates as food ingredients. 1979.

Evaluation of the health aspects of manganous salts as food ingredients. 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients. 1979.

Evaluation of the health aspects of hydrochloric acid as a food ingredient. 1979.

Evaluation of the health aspects of lecithin as a food ingredient. 1979.

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients. 1980.

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient. 1981.

Evaluation of the health aspects of methyl polysilicones as food ingredients. 1981

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of soya fatty acid amines as food ingredients. 1981.

Evaluation of the health aspects of activated carbon (charcoal) as a food processing aid. 1981.

Evaluation of the health aspects of smoke flavoring solutions and smoked yeast flavoring as food ingredients. 1981.

Evaluation of the health aspects of corn mint oil as a food ingredient. 1981.

Evaluation of the health aspects of a mixture. Evaluation of the health aspects of diferrous, dipotassium ferrous, and potassium ferrocyanides as finding agents in wine production. 1981.

Evaluation of the health aspects of wheat gluten, corn gluten, and zein as food ingredients. 1981.

Evaluation of the health aspects of peptones as food ingredients. 1981.

Evaluation of the health aspects of shellac and shellac wax as food ingredients. 1981.

Evaluation of the health aspects of sodium metasilicate and sodium zinc metasilicate as food ingredients. 1981.

Evaluation of the health aspects of oat gum, okra gum, quince seed gum, and psyllium seed husk gum as food ingredients. 1982.

Contributing Authorship on the Following Publications of the National Academy of Sciences

Principles and Procedures for Evaluating the Toxicity of Household Substances. Committee for the Revision of NAS Publication 1138, Committee on Toxicology, Assembly of Life Sciences National Research Council, National Academy of Sciences National Academy Press, Washington, D.C. 1977

Drinking Water and Health. Safe Drinking Water Committee, Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, National Academy of Sciences Volume 1, 1977; Volume 2, 1980, Volume 3, 1980 National Academy Press, Washington, D.C.

Estimating Consumer Exposure to Food Additives and Monitoring Trends in Use. Food Additives Survey Committee, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences National Academy Press, Washington, D.C. 1992

Examination of Dietary Recommendations for Salt-Cured, Smoked, and Nitrite-Preserved Foods Pariza, M.W., Borzelleca, J.F., Cassens, R.G., Filer, L.J., and Kritchevsky, D., CAST Issue Paper Number 8, November 1997

CURRICULUM VITAE

Name: John Richard Bend

Date and Place of Birth:

Citizenship: Canadian and USA

Marital Status: Married

Children:

Education:

June 1960 -	Graduated from Stonewall Collegiate Institute, Manitoba, Canada
May 1964 -	B.Sc. (Pharmacy) University of Manitoba, Canada
Feb. 1967 -	M.Sc. [Pharmaceutical Chemistry] University of Manitoba, Canada
Feb. 1971 -	Ph.D. [Pharmaceutical Chemistry (Drug Metabolism)] Sydney University, N.S.W., Australia (Thesis: A Study of the Metabolism of Two Carbamate Pesticides)

Management Training:

Nov. 2-7, 1975	Advanced Management Seminar, U.S. Civil Service Commission (50 hours)
Feb. 14-18, 1977	Introduction to Supervision, U.S. Civil Service Commission (40 hours)
Feb. 22, 1977	Supervisory Seminar on Grievances, Adverse Actions, Terminations (8 hours)
Apr. 20-21, 1978	Principles of Position Classification for Supervisors and Managers (16 hours)
Oct. 28, 1977	Workshop on The Selection Interview (8 hours)
Feb. 14, 1980	Equal Employment Opportunity Course (16 hours)
March 28, 1980	NIH Project Officer Compliance Training Course (8 hours)
May 20, 1980	Developing More Effective Supervisors. Dunn and Bradstreet (8 hours)
Dec. 6-10,1987	Executive Development Seminar, Management Education Programs, Association of American Medical Colleges

Brief Chronology of Employment:

1961	Summer Assistant, Manitoba Clinic Pharmacy, Winnipeg
1962	Summer Research Assistant, University of Manitoba, School of Pharmacy
1963	Research Assistant (summer), Defense Research Board of Canada, Defense Research Chemical Laboratories, Ottawa
1964-1966	Graduate Student, Faculty of Pharmacy, University of Manitoba
1964-1967	Registered Pharmacist, St. Norbert Pharmacy (part-time)
1966-1967	Assistant Lecturer, Faculty of Pharmacy, University of Manitoba, Canada
1967-1970	Research Student, University of Sydney, N.S.W., Australia
1970-1976	Visiting Associate, National Institute of Environmental Health Sciences (NIEHS), National Institute of Health (NIH), Research Triangle Park, North Carolina 27709
1975-1979	Head, Section of Marine Pharmacology and Biomedicine, NIEHS/NIH, Research Triangle Park, North Carolina 27709
1976-11/80	Visiting Scientist, NIEHS/NIH, Research Triangle Park, North Carolina 27709.
8/78- 8/79	Acting Chief, Laboratory of Pharmacology, NIEHS/NIH.
9/78-12/80	Head, Comparative Pharmacology Section, Laboratory of Pharmacology, NIEHS/NIH.
11/80-12/86	Research Chemist, GS-14, NIEHS/NIH.
12/80-12/86	Chief, Laboratory of Pharmacology, and Head, Molecular and Comparative Pharmacology Section, NIEHS/NIH.
9/86-12/00	Professor and Chair, Department of Pharmacology and Toxicology, Faculty of Medicine, University of Western Ontario (UWO), London, Canada N6A 5C1.
1/2/99- Date	Associate Scientist, Child Health Research Institute
7/1/96 -6/30/99	Director of Research, Faculty of Medicine & Dentistry, UWO.
7/1/99- Date	Associate Dean - Research, Faculty of Medicine & Dentistry, UWO
4/1/97 -DATE	Director, CIHR Program in Drug and Environmental Safety, Faculty of Medicine & Dentistry, UWO.

1/1/01-6/30/02	Professor, Department of Pharmacology and Toxicology, Faculty of Medicine & Dentistry, UWO.
7/1/02-12/31/04	Professor, Physiology & Pharmacology, Department of Physiology & Pharmacology, Facultry of Medicine & Dentistry, UWO.
1/1/05-Present	Professor, Pathology, Department of Physiology, Schulich School of Medicine, UWO.

Military Service: None

Societies:

Current: American Society for Pharmacology and Experimental Therapeutics
Society of Toxicology
International Society for the Study of Xenobiotics
American Association for the Advancement of Science
The Pharmacological Society of Canada
Society of Toxicology of Canada

Honors and Other Special Scientific Recognition:

1959	Medals for Chemistry and Physics (highest standing), Stonewall Collegiate Institute.
1961-1962	Isbister Scholarship (highest standing), University of Manitoba.
1962-1963	Isbister Scholarship (highest standing), University of Manitoba.
1961-1962	National Drugs Ltd. Scholarship (outstanding merit).
1962-1963	Burroughs Wellcome and Company Scholarship.
1962-1963	Manitoba Pharmaceutical Association Silver Medal (highest standing).
1962-1963	Dr. D. McDougall Memorial Scholarship (outstanding merit).
1963-1964	University of Manitoba Gold Medal (Pharmacy).
1963-1964	Manitoba Pharmaceutical Association Gold Medal.
1963-1964	Flexon Silver Medal (highest standing, Organic Pharmaceutical Chemistry).
1964-1966	National Research Council of Canada Fellow (for M.Sc. Degree).
1967-1970	British Commonwealth Scholar (for Ph.D. Degree).
1977-Date	Member, Editorial Advisory Board for Drug Metabolism and Disposition.
1977-Date	Associate Editor, Reviews in Biochemical Toxicology.
1978	Nominated for John J. Abel Award in Pharmacology (American Society of Pharmacology and Experimental Therapeutics).
1/78-12/86	Editor, for the Americas, Chemico-Biological Interactions.
1980-1981	Associate Editor, Metabolic Basis of Detoxication.
1982-1993	Board of Editors, Environmental Health Perspectives.
1984-1990	Member, Editorial Board of Toxicology and Industrial Health.
6/16/86	Received the NIH Directors Award "for significant leadership in management of the Laboratory of Pharmacology and development of scientific programs at the forefront of research on mechanisms of toxication-detoxication". This is the highest honor award given by NIH.
1988-1991	Councillor (elected), International Society for the Study of Xenobiotics.
1988-1990	Member, Review Panel G, National Cancer Institute of Canada.
1988-1992	Member, Pharmacology and Toxicology Review Panel, Medical Research Council of Canada (MRC).
1/90-12/97	Associate Editor of the Canadian Journal of Physiology and Pharmacology.
Jan. 1990	Elected Vice-President, Society of Toxicology of Canada; served as Vice-President for 1990-1, as President for 1992-3 and as Past-President for 1994 and 1995.
1991	Elected, Vice-President, Mechanisms Section, Society of Toxicology; served as Vice-President for 1991, President for 1992 and Past-President for 1993.
1991-1994	Member, Scientific Program Committee, 12th International Congress of Pharmacology, Montreal from July 22-29, 1994.
1991-1994	Chairman, Scientific Program Committee for the 10th International Symposium on Microsomes and Drug Oxidations, July 18-21, 1994 in Toronto. Official satellite meeting of the 12th International Congress of Pharmacology.
1992-1997	Member (appointed by MRC) to the Eco-Research Council of Canada, a Government of Canada review panel for large interdisciplinary (natural sciences and engineering, social sciences and medical sciences) research grants submitted as part of the Green Plan.

1992-1995	Member, Canadian National Research Council-International Union of Pharmacology Committee.
Jan. 1993	Appointed to the Editorial Advisory Board of Journal of Biochemical Toxicology.
Jan. 1993	Appointed to the Editorial Advisory Board of Xenobiotica.
Feb, 1993 - Present	Member, Province of Ontario Pesticide Advisory Committee, Ministry of Energy and theEnvironment, Province of Ontario; Chair, Pesticide Classification Sub-Committee; Vice-Chair, Research Sub-Committee.
7/93-8/94	Heart and Stroke Foundation of Canada representative on Canadian Council of Animal Care.
1994-1997	Councillor (elected), International Society for the Study of Xenobiotics.
June, 1994	Chair, Site Visit Review Team, Eco-Research Council of Canada to the University of Victoria to evaluate the proposed Chair in Environmental Law and Policy.
May, 1996	Received Dean, Faculty of Medicine, UWO, Award of Excellence for performance in Research and Administration.
1996-2005	Faculty of Medicine & Dentistry Representative to the Research and Graduate Studies Subcommmittee of the Association of Canadian Medial Colleges (ACMC).
1998-2002	Member, Persistent Organic Pollutants (POPs) review panel of the Toxic Substances Research Initiative, Health Canada and Environment Canada
1999-present	Member, World Health Organization Expert Panel on Food Additives
1999-2005	Association of Canadian Medical Colleges/Faculties of Canadian Med representative to the Canadian Council on Animal Care
2000	Canadian Paediatric Clinical Pharmacology Network Workshop, Westin Hotel, Ottawa. April 8-9. Co-applicant on CIHR New Opportunities grant that established this network with Michael Rieder (PI).
2000	Co-applicant with Fred Longstaffe (PI) and several others including Michael Rieder of a successful CFI infrastructure award for "Stable Isotope Science Western". Clinical pharmacology component includes use of stable isotopes for measuring rates of in vivo drug metabolism non-invasively.
2001	Invited speaker, Annual Meeting of the Pharmacological Society of Canada in the Symposium titled "Regulation of the activity and expression of cytochrome P450", Vancouver, March 29, 2001.
2001	Member, NSERC Site Visit team to the University of Britsh Columbia for the research network on Herbal Medicine., Sept. 6-8, 2001.
2001	Member, Peer Review Committee of the Health Canada Chief Scientist Competition, Ottawa, Nov. 21, 2001.
2001	Second meeting of the CIHR-funded CanadianConsortium for Drug and Environmental Safety, of which I am the Director. I was the PI of the CIHR-New Opportunities grant that established this Consortium.
2001-Present	Member, Rx&D Health Research Foundation Advisory Council.
2001-2002	Vice-Chair, Canadian Council on Animal Care
2002	Chairman, Peer Review Committee of the Health Canada Chief Scientist Competition, Ottawa, Jan. 9-11, 2002.
2002	Invited participant, Health Canada Conference of Pharmaceuticals and personal care products in th environment.. Niagara-on-the-Lake, Feb. 24-27, 2002.
2002-Present	Member, CIHR Environment and Health Steering Committee, since it was established in March , 2002 .
2002	External Reviewer, Department of Pharmacology, University of Montreal, May 12-15, 2002.
2002	Member, CIHR Panel of Pharmaceutical Sciences, Ottawa, May 15-17, 2002.
2002	Chairman, Peer Review Committee of the Health Canada Chief Scientist Competition, Ottawa, Oct. 17-18, 2002
Nov, 2002 Present	Member, Advisory Committee to Minister of Health on Chemical, Biological, Radiological and Nuclear (CBRN) Safety, Security and Research.
Dec, 2002-Present	External Reviewer, Defence Research and Development Canada CBRN Research and Technology Initiative.
2002-2003	Chair, Canadian Council on Animal Care
2004	Speaker, CIHR Workshop of Reproductive and developmental toxicology research. Sponsored by Canadian Institute of Human Development, Child and Youth Health (Barbara Hales, PI; Jack Bend; Gideon Koren; Bruce Murphy, co-applicants).
2004-2005	Past-Chair, Canadian Council on Animal Care.
2005	Invited Guest, Third Meeting, Consortium for the Globalization of Chinese Medicine, Hong Kong, January 29-31, 2005. As a result of the invited presentation I gave there, Western was

invited to become the first Canadian member of the CGCM, joining more than 30other universities from China, Hong Kong, Taiwan and the United States.

2005 Member, Infrastructure Review Committee, Fonds de la recherché en sante Quebec, Feb. 4-5, 2005.

Research Interests:

Reactive metabolites of xenobiotics and endobiotics. Current specific interests include the development of isozyme-selective, tissue-selective mechanism-based inhibitors of cytochrome P450 monooxygenases; understanding the mechanisms responsible for cell and tissue selective/specific, isozyme selective modulation of P450 monooxygenases by chemical pollutant inducers and physiological/pathobiological stimuli; the pathobiology of up-regulation of P4501A1 in extrahepatic tissues including lungs, kidney and heart; and drug-drug and food-drug interactions dependent upon inhibition of human P4501A and/or 3A isozymes. Most recently, detailed investigations of the mechanisms by which antioxidants such as bilirubin cause apoptosis, in cluding by oxidative stress.

Committees, Adjunct Appointments, External Reviews:

Feb. 13-14, 1975	Member, Organizing Committee, Meeting on Marine Biomedical Research, Smithsonian Institute, Washington, D.C.
1975-1980	Alternate NIEHS Representative, USA National AdvisoryCommittee on Oceans and Atmosphere.
1975-1981	Trustee, Mt. Desert Island Biological Laboratory, Salsbury Cove, Maine.
1976-1983	Visiting Scientist, C.V. Whitney Laboratory, University of Florida, St.Augustine, Florida.
1976-1979	Member, Committee on Environmental Pharmacology, American Society for Pharmacology and Experimental Therapeutics.
Feb. 9-11, 1976	Member, Organizing Committee, Symposium on the Role of Metabolic Activation in Producing Mutagenic and Carcinogenic Environmental Chemicals, Research Triangle Park, N.C.
May 14-16, 1976	External Reviewer, Biological Effects Program, National Science Foundation's International Decade of Ocean Exploration, Texas A and M University, College Station, Texas.
1975-1976	Member, Search Committee for Chief, Laboratory of Pharmacology, NIEHS.
10/77-6/78	Member, Committee on Laboratory Space, Intramural Research Program, NIEHS.
11/29-12/2/77	External Reviewer, National Oceanic and Atmospheric Administration (NOAA, Dept. of Commerce), Outer Continental Shelf Environmental Assessment Program, Northwest Alaska Fisheries Center, Seattle, Washington.
1977-1978	Chairman, Search Committee for Chief, Laboratory of Animal Genetics, NIEHS, Research Triangle Park, NC.
7/1/81-7/1/84	Adjunct Associate Professor, School of Agriculture and Life Sciences, North Carolina State University, Raleigh, NC.
7/1/84-12/31/86	Adjunct Professor, School of Agriculture and Life Sciences, North Carolina State University, Raleigh, NC.
July 23-26, 1978	Member, Scientific Committee for "Conjugation Reactions in Drug Biotransformation", Satellite Symposium (of the 7th International Congress of Pharmacology) held in Turku, Finland.
8/78-6/81	NIEHS Coordinator, Special Topics in Toxicology, Research Triangle Park Graduate Course in Toxicology.
Aug. 7-11, 1978	Session Chairman and Speaker, Gordon Conference on Drug Metabolism, Holderness School, Plymouth, N.H.
1/79-8/79	Member, Search Committee for Chief, Laboratory of Organ Function and Toxicology, NIEHS.
May 10, 1979	Moderator and Organizer, NIH Science Writers Seminar on "Toxication or Detoxication of Environmental Chemicals", Bethesda, MD.
8/1/79-12/31/86	Adjunct Member, Toxicology Faculty, North Carolina State University, Raleigh, N.C.
Aug. 21, 1979	Organizer, Symposium on "Aquatic Animals as Models in Biomedical Research" held at the American Society of Pharmacology and Experimental Therapeutics, Fall meeting.
10/79-10/83	Member, Executive Committee, Toxicology Faculty, North Carolina State University, Raleigh, N.C.
1/1/80-12/31/82	Chairman, Radiation Safety Committee, NIEHS.
7/14/80-7/31/82	Member, Scientific Advisory Committee of the Mount Desert Island Biological Laboratory, Salsbury Cove, ME.
10/1/80-6/30/85	Adjunct Associate Professor, Curriculum in Toxicology, School of Medicine, University of North Carolina at Chapel Hill.
7/1/85-12/31/86	Adjunct Professor, Curriculum in Toxicology, School of Medicine, University of North Carolina at Chapel Hill.
7/81-7/82	Chairman, Scientific Advisory Committee of the Mount Desert Island Biological Laboratory, Salsbury Cove, ME.
4/27/81-12/84	Member, Organizing Committee for Section on Toxicology in American Society of Pharmacology and Experimental Therapeutics.
3/82-11/86	Chairman, Laboratory Special Promotion Committee (GS 9-11, GS 11-12), NIEHS.
10/82-9/83	Member, Search Committee for Mammalian Molecular Genetics Section, Laboratory of Genetics, NIEHS.
10/83-12/86	Member, Examination Committee, Toxicology Faculty, North Carolina State University.
3/84-12/86	Reviewer, Innovation Research Fund Proposals, State of North Carolina.
11/7/84-11/9/84	Medical Research Council of Canada Visiting Professor, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver.

8/85-12/86	Chairman, Committee for Organization of Hans L. Falk Memorial Lecture Series at NIEHS.
10/85-12/86	Member, Curriculum Committee, Toxicology Faculty, North Carolina State University.
3/86-12/86	Referee, Competitive Grants Program, North Carolina Biotechnology Center.
6/25-7/12/87	Visiting Professor, University of Siena, Italy.
Nov. 8-13, 1987	Member, Program Committee for Joint International Society for Study of Xenobiotics/U.S. Society of Toxicology Symposium on "Endogenous Factors in The Toxicity of Xenobiotics", Clearwater, Florida. Organized and chaired the session dealing with "Conjugation Enzymes".
Nov.-Dec., 1987	Consultant, Monsanto Agricultural Company, St. Louis, Missouri.
June 14-16, 1988	Consultant, NIH Site Visit to Oregon State University, Corvallis.
June, 1989	Judge, Pharmacological Society of Canada Graduate Student Awards for presented paper, CFBS.
June, 1989	Invited Member (one of five) by Pharmacological Society of Canada to attend Workshop on Media Relations, CFBS.
June, 1989	Organizer, Symposium on Regulation of Cytochrome P450 Isozymes Important in the Metabolism of Endogenous Substrates, CFBS.
Nov.14-16, 1989	External Reviewer, MRC Site Visit of the Bureau of Drug Research, Health and Welfare, Canada.
Nov.'89-Nov.'90	Member, "Toxicology and Therapy of Intoxications" Subcommittee, Association for Medical School Pharmacology.
June, 1990	Judge, Pharmacological Society of Canada Graduate Student Awards for best paper, CFBS.
5/28-6/2/90	External Reviewer, Environmental Health Sciences Center Research Programs, Oregon State University.
Feb. 4-6, 1991	NIEHS/NIH Site Visit, University of Wisconsin, Milwaukee.
June 1991 - 1994	University of Guelph, Centre for Toxicology Management Committee.
March 5, 1991	External Reviewer, Career Scientist Award, Ontario Ministry of Health, Queen's University.
June 9, 1991	Organizer, Canadian Federation of Biological Societies (CFBS) President's Symposium on Global Change held at Queen's University.
Sept.11-13, 1991	Member, Review Team on Animal Care at Dalhousie (Review organized by President, Dalhousie University).
Jan.,'92- Dec.'94	Member (elected) Executive Committee, Drug Metabolism Division, American Society of Pharmacology and Experimental Therapeutics.
May,1993 - Now	Member, Scientific Advisory Board, Drug Safety Research Group, University of Toronto.
May-July, 1993	Member, Ad hoc Advisory Committee to Discuss Testing of Impurities in New Drug Substances, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.
July, 1993	Eternal Reviewer for Department of Pharmacology, University of Toronto prior to appointment of Chair.
July 27, 1994	Chair, Plenary Lecture of Dr. Stanley Crooke at the XIIth International Congress of Pharmacology, Montreal Congress Centre.
April,'94	Consultant, Schering Drug Company re Claritin.
May 5-6, 1994	External Reviewer of Faculty of Pharmacy, University of Toronto for Ontario Council of Graduate Studies.
June, '94 - Now	Member, Scientific Advisory Board for the Superfund Program Project Grant of the Department of Public Health and Community Medicine, Department of Environmental Health, University of Washington.
July, 1994	Appointed Co-Chair, Symposium on Biomarkers for Chemical Exposure, International Union of Toxicology Meeting, July 2-5, 1995, Seattle.
Sept, 1996	External reviewer, Ph.D. examination of James McNamee, Department of Pharmacology and Toxicology, Queen's University.
Dec, 1996	External reviewer, Ph.D. examination of Reza Anari, University of Toronto.
Jan, 1997	Chair, Tri-Council site visit to University of Victoria Eco-Research Chair Program.
July, 2000	External reviewer, PhD examination of Gonzalo J. Diaz, University of Guelph

Referee for Journal of Pharmacology and Experimental Therapeutics, Molecular Pharmacology, Biochemical Pharmacology, Chemical Research in Toxicology, Cancer Research, Archives of Biochemistry and Biophysics, Science, Endocrinology, Life Sciences, Toxicology and Applied Pharmacology, Chemico-Biological Interactions, Drug Metabolism and Disposition, Analytical Biochemistry, Experimental Lung Research, Marine Research, Canadian Journal of Physiology and Pharmacology, Canadian Journal of Fisheries and Aquatic Sciences, Xenobiotica and for grant/contract applications by U.S. National Cancer Institute, U.S. National Science Foundation, U.S. Department of Commerce (Sea Grant), U.S. Environmental Protection Agency, American Cancer Society, Medical Research Council of Canada, Ontario Thoracic Society, National Sciences and Engineering Research Council of Canada, the Sunnybrook Medical Centre, the Australian Research Council, Canadian Cystic Fibrosis Foundation and the British Columbia Health Care Research Foundation.

Contract Officer:

Contract Officer, N01-ES-2101, The Carcinogenic Effects of Petroleum Hydrocarbons on Selected Marine and Estuarine Organisms (Terminated 1/80).

Assistant Contract Officer, N01-ES-6-2124, Tier I Microsomal Assay for Mutagenesis (Terminated 9/77).

University of Western Ontario (UWO)

UWO Committees:

- Member, Biosafety Committee, UWO (Feb. 1987 - July 1996)
- Member, Advisory Board, UWO Occupational Health & Resources Centre (1986 -1992)
- Member, UWO Senate Committee on University Planning (SCUP), Subcommittee on Priorities in Academic Development (SUPAD) (July 1987 - June 1990); Chairman, SUPAD, July 1988 - June 1990)
- Member, Biology Colloquium Committee (March 1987 - 1992)
- Member, UWO Selection Committee, Ontario Ministry of Health Trillium Scientist Award (September 1991-present).
- Member, Search Committee for Dean, Faculty of Journalism, April 15, 1993 to April 6, 1994.
- Member, UWO Senate Committee on University Planning (SCUP); initial forum for debate on relative merits of retention/dissolution of Faculty of Journalism; reviews of financial requirements/special requests for funding recommended by the Vice-Provost (July, 1993- November, 1994).
- Member and Vice-Chair, Senate Committee on University Development (SCUD); elected representative of the Faculty of Medicine; debate and/or approve/disapprove recommendations concerning Campus Master Plan as well as other plans for facility replacement or renovation (July, 1993 - November, 1994).
- Faculty of Medicine Representative, University-wide Committee to establish UWO Senate-approved Research Centre for Renewal of the Global Environment (1992-1994).
- Member, SUPAD and Chair, Biosciences Review Group, November 1993 - March, 1996.
- Reviewer, proposal to establish a Type 3 Research Centre (the Tribology Research Centre) in the Faculty of Engineering Science, May, 1994.
- Elected Member (1 of 4 elected faculty members), UWO President's Strategic Planning Task Force, October, 1994 - Present.
- Invited Faculty Member and Facilitator, 2nd Annual Powers of Partnership Conference, Organized by UWO University Students' Council, December 3, 1994.
- University Research Board, July 1, 1996 - present.
- Sub-Committee, URB for Canada Foundation for Innovation applications, Aug., 1997 - present.
- UWO Committee for Canada Research Chairs, April, 2000 - present

Committees, Faculty and Department:

- Member, Search Committee, Ciba-Geigy Clinical Pharmacologist, Robart's Research Institute (Sept. 1986 - April 1987).
- Member, UWO Faculty of Medicine Executive Committee (Sept. 1986 - June 30, 1997); UWO Faculty of Medicine & Dentistry Executive Committee (July 1, 1997 - present).
- Member, UWO Faculty of Dentistry Council (Sept. 1986 - present)
- Chairman, Appointments, Tenure and Promotion Committee, Dept. of Pharmacology and Toxicology (Sept., 1986-present).
- Member, (ex officio), Graduate Studies Committee, Dept. of Pharmacology and Toxicology (1986 - present)
- Member, Curriculum Committee, Department of Pharmacology and Toxicology (Sept. 1986 - present)
- Chairman, Executive Committee, Department of Pharmacology and Toxicology (Sept. 1986 - present)
- Member, Stewart Task Force on Undergraduate Education in the Basic Health Sciences (Aug., 1987 - May, 1988)
- Member, Search Committee, Chairman, Dept. of Anaesthesiology (May 1987 - Sept. 1987).
- Member, Ad hoc Committee on Computer-assisted Education, Dept. of Pharmacology and Toxicology (Jan., 1987 - July, 1988).
- Member, Safety Committee, Dept. of Pharmacology and Toxicology (July 1987 - present)
- Member, UWO Faculty of Dentistry Executive Committee (May 1988 - present)
- Member, Steering Committee for Computer-based Learning Development (November 1988 - 1990)
- Member, UWO Faculty of Science Educational Policy Committee (July 1988 - June 1990)
- Member, Faculty of Medicine, Budget & Finance Committee (May 1989 - June 1992).
- Chairman, Task Force on AIDS-Related Research, Faculty of Medicine (Nov. 1989 - Dec. 1992).
- Member, Faculty of Medicine Promotion and Tenure Committee, 1990 - 1993.
- Member, Faculty of Science Executive Committee, 1990-1996

- Joint Selection Committee for the Director of the Lawson Research Institute, UWO, Jan.'93
- Member, Search Committee, A.C. Burton Vascular Biology Laboratory research scientist, Victoria Hospital, March, 1993 - April, 1994
- Member, Faculty of Medicine Planning and Priorities Task Force, June 1993 to March 1994.
- Member, Task Force on Annual Agreement and Review of Performance, June 1993 to June, 1994.
- Reviewer, UWO Type 3 Research Centre for Senate Committee on University Planning, April-May, 1994.
- Chair, Basic Health Sciences Committee, Faculty of Medicine, July, 1994 to June, 1995.
- Co-leader, Workshop on Internal Research Funding, Faculty of Medicine Research, June, 1994.
- Member, UWO Faculty of Medicine Committee to initiate formal MD/PhD Program, May - November, 1994.
- Member, Faculty of Medicine Implementation Committee - charged with setting criteria for selective budget reallocations; recommendations to be made to Faculty of Medicine Executive Committee; Sept., 1994 to Feb., 1995.
- Delegate representing Basic Scientists in the Faculty of Medicine at discussions with Province of Ontario concerning Alternate Funding Plan for UWO Faculty of Medicine, July, 1994 - June, 1995.
- Member, Faculty of Medicine Planning and Priorities Task Force, 1994-1995.
- Member, Faculty of Medicine Task Force on Annual Agreement and Review of Performance, 1994-95.
- Member, Search Committee, Chair of Anatomy, 1994-95.
- Member, Faculty of Medicine Implementation Advisory Committee, 1994-95.
- Co-leader with Dr. Peter Canham, Workshop on Internal Funding, Faculty of Medicine Reseach Day.
- Member, Faculty of Medicine Appointments and Remuneration Task Force, Phase II, 1994-96.
- Organizer, Session on Research Funding from Drug Companies, Faculty of Medicine Research Days, May, 1995.

UWO Teaching:

1986 - 87
- Drugs and Enzymes 466b/566b - gave 6 hours of lectures.
- Medical Pharmacology - gave 2 hours of lectures on Drug Metabolism
- Pharmacology & Toxicology 441y, Seminar/Essay fourth year honors course; attended 15 classes; served as co-ordinator of toxicology topics and seminar/essay advisor for 6 students.
- Graduate Seminar Course 541y/610 - Course Co-manager.
- Pharmacology Research Seminar Series - organized this seminar series.

1987 - 88
- Biology 362, Introduction to Pharmacology and Toxicology for Third Year Science students - gave 6 hours of lectures.
- Nursing 106 - Nursing Pharmacology - gave 6 hours of lectures.
- Pharmacology & Toxicology 441y - Toxicology Coordinator; attended all toxicology sessions.
- Principles of Pharmacology 462a - Course Coordinator; gave 6 hours of lecture.
- Medical Pharmacology - gave 5 hours of lectures.
- Pharmacology 106 - gave 6 hours of lecture.
- Graduate Seminar Course 541y/610 - Course Co-Manager; attended all sessions.
- Pharmacology 480/481 - extensive laboratory course for fourth year honors students; developed/ supervised labs in iochemical pharmacology requiring 2 weeks (22hr) to complete.

1988 - 89
- Pharmacology for Nurses 106 - gave 6 hours of lectures.
- Biology 362 - gave 6 hours of lectures.
- Pharmacology & Toxicology 441y - Toxicology Coordinator; attended all toxicology sessions.
- Principles of Pharmacology 462a - Course Coordinator; gave 6 hours of lectures.
- Pharmacology & Toxicology 480 - developed/supervised labs (32 hours).
- Medical Pharmacology - gave 4 hours of lectures.
- Graduate Seminar Course 541y/610 - Course Manager; attended all sessions.

1989 - 92
- Pharmacology for Nurses 106 - gave 6 hours of lectures.
- Biology 362 - gave 6 hours of lectures.
- Pharmacology & Toxicology 441y - Toxicology Coordinator and Course Coordinator; attended all toxicology sessions.
- Pharmacology & Toxicology 462a - Course Coordinator; gave 6 hours of lecture.
- Pharmacology & Toxicology 480 - lab instructor - 24 hrs.; supervised 1 research project.
- Medical Pharmacology - gave 4 hours of lectures.
- Graduate Seminar Course 541y/610 - attended all sessions.

1992 - 94
- Pharmacology for Nurses 106 - gave 6 hours of lectures.
- Biology 362 - gave 6 hours of lectures.
- Pharmacology & Toxicology 441y - Toxicology Coordinator and Course Coordinator; attended all toxicology sessions.
- Pharmacology & Toxicology 462a - Course Coordinator; gave 6 hours of lecture.
- Pharmacology & Toxicology 480 - lab instructor - 24 hrs.; supervised 1 research project.
- Medical Pharmacology - gave 5 hours of lectures.
- Graduate Seminar Course 541y/610 - attended all sessions.
- Advanced Graduate Course in Carcinogenesis - 2 lectures.

1994-95
- Lectured (5 hours) in Medical Pharmacology
- Co-ordinated Pharmacology 462A, Principles of Pharmacology, and gave 6 hours of lectures. Collected all of the materials to have the course evaluated by the Department Curriculum Committee.
- Unable to co-ordinate, with Professor John Hamilton, Pharmacology 441Y, seminar and essay course on special topics in pharmacology and toxicology this year because it is held on Friday morning. Contributed to organizing the course and attended all possible sessions when not at Faculty of Medicine administrative meetings.
- Continued to be regular attendee/contributor to Pharmacology 541Y and Pharmacology 610, graduate courses (seminars, literature critiques, grant application preparation and defense, essays) in our department.
- Lectured in Biology 362 (6 hours per year).
- Prepared 4 hours of lecture material for Pharmacology 555, our new graduate course in advanced concepts that will replaced our M.Sc. comprehensive examination.

1995-96
- Lectured (5 hours) in Medical Pharmacology (second year Medicine).
- Co-ordinated Pharmacology 462A, Principles of Pharmacology, and gave 6 hours of lectures.
- Unable to co-ordinate, with Professor John Hamilton, Pharmacology 441Y, seminar and essay course on special topics in pharmacology and toxicology this year because it is held on Friday morning. Contributed to organizing the course and attended all possible sessions when not at Faculty of Medicine administrative meetings.
- Continued to be regular attendee/contributor to Pharmacology 541Y and Pharmacology 610, graduate courses (seminars, literature critiques, grant application preparation and defense, essays) in our department.
- Lectured in Biology 362 (6 hours per year).
- Prepared 4 hours of lecture material for Pharmacology 555, our new graduate course in advanced concepts that will replaced our M.Sc. comprehensive examination.
- Lectured 2 hours in Department of Pathology graduate course in Biology of Human Cancer.
- Lectured on Biomarkers in graduate course in Environmental Sciences.

1996-97 Study leave - no teaching responsibilities. Maintained research program and acted as Director of Research for the Faculty of Medicine & Dentistry.

1997-98 - Lectured (5 hours) in Medical Pharmacology (second year Medicine).
- Lectured in Pharmacology 462A, Principles of Pharmacology, and gave 6 hours of lectures.
- Continued to be regular attendee/contributor to Pharmacology 541Y and Pharmacology 610, graduate courses (seminars, literature critiques, grant application preparation and defense, essays) in our department.
- Lectured 2 hours in Department of Pathology graduate course in Biology of Human Cancer.
- Lectured on metabolic activation in graduate course in Environmental Science (2 hrs).
- Lectured 2 hours in new curriculum, Faculty of Medicine (Drug Metabolism).

1998-99 - Lectured (5 hours) in Medical Pharmacology (second year Medicine).
- Lectured in Pharmacology 462A, Principles of Pharmacology, and gave 6 hours of lectures.
- Continued to be regular attendee/contributor to Pharmacology 541Y and Pharmacology 610, graduate courses (seminars, literature critiques, grant application preparation and defense, essays) in our department.

1999-00 - Lectured 4 hours) in Medical Pharmacology (second year Medicine).
- Lectured in Pharmacology 462A, Principles of Pharmacology, and gave 6 hours of lectures.
- Continued to be regular attendee/contributor to Pharmacology 541Y and Pharmacology 610, graduate courses (seminars, literature critiques, grant application preparation and defense, essays) in our department.
- Lectured 2 hours in Department of Pathology graduate course in Biology of Human Cancer.

Graduate Student Supervision:

Jennifer Van Anda, Ph.D., 1978, Pharmacology, University of North Carolina, Chapel Hill. Supervisor. All of the research for Jennifer's dissertation was done in my laboratory at NIEHS.

Gary L. Foureman, Ph.D., 1982, Toxicology Curriculum, North Carolina State University, 1982. Ssupervisor. All of the research for Gary's dissertation was done in my laboratory at NIEHS.

Craig Harris, Ph.D., 1985, Curriculum in Toxicology, University of North Carolina, 1984. Major co-supervisor along with Dr. Ron Thurman. Approximately 50% of Craig's research was done in my laboratory at NIEHS and the rest was done at Ron's in the Department of Pharmacology at UNC.

Michael W.H. Coughtrie, Ph.D., 1986, Biochemistry (U. of Dundee, Scotland), Sept. 1984 - Dec. 1986. Much of the research for his Ph.D. was conducted in my laboratory at NIEHS while he was an international visitor; co-supervisor with Dr. Brian Burchell, University of Dundee.

Leah Christine Knickle, Ph.D., 1993, Pharmacology and Toxiology. Supported throughout studies by an Ontario Graduate Scholarship. Winner of UWO Nellie Farthing Award, 1992-93. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 1991-92. Supervisor.

Kimberley Janine Woodcroft, Ph.D. 1993, Pharmacology and Toxicology. Supported throughout studies by MRC Studentship. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 1990-91. Supervisor.

Claudio Munoz, M.D. received his M.Sc. in Pharmacology and Toxicology, 1993. Co-supervisor with Dr. David Spence.

Susan E. Rau, received her M.Sc. in Pharmacology and Toxicology in 1995. Co-supervisor with Dr. David Bailey.

Felicia So, received her M.Sc. in Pharmacology and Toxicology in 1996. Co-Supervisor with Dr. Ken Carroll.

Christopher J. Sinal, received his Ph.D. in Pharmacology and Toxicology in 1998. Supported throughout studies by Ontario Graduate Scholarship. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 1994-95. Winner of MRC Post-doctoral Fellowship, 1998-2001. Supervisor

Gordon P. McCallum received his Ph.D. in Pharmacology and Toxicology in 1999. Supported by a MRC Studentship. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 1993-94. Supervisor.

Maria Ricci received her M.Sc. In Pharmacology & Toxicology in 2000. Co-supervised with Drs. Jim Xuan and Jim Koropatnick.

Elliott Offman received his M.Sc in Pharmacology & Toxicology in 2000. Co-supervised with David Bailey and David Freeman.

Jeremy Scott received his PhD in 2001. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 1998-99. Co-Supervised with David McCormack.

John Seubert received his PhD in 2002. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 2001-2002. Awarded an Ontario Government Scholarship during 1998-2002. Supervisor.

Claudio Munoz, M.D., M.Sc received his PhD in 2002.. Co-Supervised with David Spence.

Asma Yaghi received her PhD in 2002. Winner of Sharma Award as best graduate student in Department of Pharmacology & Toxicology in 2000-2000. Co-Supervisor (with David McCormack).

Chad Yaremko received his MSc in 2002. Supervisor.

George Dresser, M.D. received his PhD in 2002. Co-supervisor with David Bailey.

Luke Martin-McCaffrey received his PhD in 2005. Characterization of regulators of G-protein signalling (RGS) 12 and 14 in mouse embryogenesis and cell division. Co-supervisor (with Tony D'Souza, primary supervisor).

Supervisor of **Garth Oakes**, a PhD student in the Pharmacology & Toxicology Graduate Program of the Department of Physiology & Pharmacology.

Supervisor of **Lorig Sarkissian**, a MSc student in the Pharmacology & Toxicology Graduate Program of the Department of Physiology & Pharmacology.

External Examiner, Graduate Students:

Steven Lieder, Ph.D., Department of Pharmacology, University of Toronto, June - July, 1989.

D.S. Riddick, Ph.D., Dept. Pharmacology and Toxicology, Queen's University, June - August, 1989.

R.F. Omar, M.Sc., Department of Biochemistry, Memorial University of Newfoundland, 1990.

A.E. Crib, Ph.D., Department of Pharmacology, University of Toronto, January 23, 1991.

R.F. Tyndale, Ph.D., Department of Pharmacology, University of Toronto, September 6, 1991.

J.P. McNamee, Ph.D., Department of Pharmacology and Toxicology, Queen's University, September 9, 1996.

M.R. Anari, Ph.D., Faculty of Pharmacy, University of Toronto, December 16, 1996.

G.J. Diaz, PhD, Department of Animal and Poultry Science, University of Guelph, July 6, 2000.

S.G.W. Wang, PhD, Department of Pharmacology & Toxicology, Queen's University, October 17, 2000.

Y. E. Timsit, PhD, University of Toronto, August 22, 2002

Post-Doctoral Research Supervision:

More than 25 post-doctoral researchers supervised while at NIEHS/NIH. At UWO, Edward W. Szczepan (1987-88), K. Cameron Falkner 1990-93) Ming Yao (1995-97), Ayman El-Kadi (1999-2002); Virginia Castro (1999-2000); Arnulfo Albores (2004-2005).

Research Operating Grants: REMOVED

[redacted]

PUBLICATIONS

THESIS

Bend, J.R.: The synthesis of compounds analogous to trans-9-oxo-2-decenoic acid (Queen Bee substance). M.Sc. Thesis, University of Manitoba, 1967.

Bend, J.R.: A study of the metabolism of two carbamate pesticides in the rat. Doctoral Thesis, University of Sydney, 1970.

MANUSCRIPTS

Bend, J.R., Holder, G.M., Protos, Eva and Ryan, A.J.: The metabolism of carbaryl (1-naphthyl N-methylcarbamate) in the cattle tick Boophilus microplus (Canestrini). Australian J. Biol. Sciences 23: 361-367, 1970.

Bend, J.R., Holder, G.M., and Ryan, A.J.: Metabolism of propham (isopropyl N-phenylcarbamate) in the rat. Food Cosmetic Toxicol. 9: 169-177, 1971.

Bend, J.R., Holder, G.M., Protos, Eva and Ryan, A.J.: Carbaryl (1-naphthyl N-methylcarbamate) metabolism in the rat and mouse: Water soluble metabolities. Australian J. Biol. Sciences 24: 535-546, 1971.

Hood, G.E.R., Bend, J.R., Hoel, D., Fouts, J.R. and Gram, T.E.: Preparation of lung microsomes and a comparison of the distribution of enzymes between subcellular fractions of rabbit lung and liver. J. Pharmacol. Expt. Ther. 182: 474-490, 1972.

Bend, J.R., Hook, G.E.R., Easterling R.E., Gram, T.E. and Fouts, J.R.: A comparative study of the hepatic and pulmonary microsomal mixed-function oxidase systems in the rabbit. J. Pharmacol. Expt. Ther. 183: 206-217, 1972.

Hook, G.E.R., Bend, J.R. and Fouts, J.R.: Mixed-function oxidases and the alveolar macrophage. Biochem. Pharmacol. 21: 3267-3277, 1972.

Hook, G.E.R., Bend, J.R. and Fouts, J.R.: The effect of some biphenyl solubilizing and suspending agents on biphenyl 4-hydroxylase of rabbit liver microsomes. Chem.-Biol. Inter. 7: 205-222, 1973.

Lucier, G.W., McDaniel, O.S., Bend, J.R. and Faeder, E.: Effects of hycanthone and two of its chlorinated analogs on hepatic microsomes. J. Pharmacol. Expt. Ther. 186: 416-424, 1973.

Drew, R.T., Gupta, B.N., Bend, J.R. and Hook, G.E.R.: Inhalation studies with a glycol complex of aluminum-chloride-hydroxide. Arch. Environ. Hlth. 28: 321-326, 1974.

Law, F.C.P., Eling, T.E., Bend, J.R. and Fouts, J.R.: Metabolism of xenobiotics by the isolated perfused lung: Comparison with in vitro incubations. Drug. Metab. Disp. 2: 433-443, 1974.

Pohl, R.J., Bend, J.R., Guarino, A.M. and Fouts, J.R.: Hepatic microsomal mixed-function oxidase activity of several marine species from coastal Maine. Drug. Metab. Disp. 2: 545-555, 1974.

Solomon, R.J., Silva, P., Bend, J.R. and Epstein, F.H.: Thiocyanate inhibition of ATPase and its relationship to anion transport. Am. J. Physiol. 229: 801-806,1975.

Philpot, R.M. and Bend, J.R.: Benzpyrene hydroxylase activity in hepatic microsomal and solubilized systems containing rabbit or rat cytochrome P-448 or P-450. Life Sci. 16: 985-998, 1975.

James, M.O., Fouts, J.R. and Bend, J.R: Hepatic and extrahepatic in vitro metabolism of an epoxide (8- ^{14}C-styrene oxide) in the rabbit. Biochem. Pharmacol. 25: 187-193, 1976

Hook, G.E.R. and Bend, J.R.: Pulmonary metabolism of xenobiotics. Invited minireview. Life Sci. 18: 279-290, 1976.

James, M.O. and Bend, J.E.: Taurine conjugation of 2,4-dichlorophenoxyacetic acid and phenylacetic acid as a major metabolic pathway in two marine species. Xenobiotica 6: 393-398,1976.

Ryan, A.J., James, M.O.,Ben-Zvi, Z., Law, F.C.P. and Bend, J.R.: Hepatic and extrahepatic metabolism of ^{14}C-styrene oxide. Environ. Hlth. Persp. 17: 135-144, 1976.

James, M.O., Foureman, G.L., Law, F.C. P. and Bend, J.R.: Perinatal development of epoxide-metabolizing enzyme activities of guinea pig and rabbit. Drug Metab. Disp. 5: 19- 28, 1977.

Ryan, A.J. and Bend, J.R.: Metabolism of styrene oxide in the isolated perfused rat liver: Identification and quantitation of major metabolites. Drug Metab. Disp. 5: 363-367, 1977.

Bend, J.R., Miller, D.S., Kinter, W.B. and Peakall, D.B.: DDE-Induced microsomal mixed-function oxidases in the puffin (Fratercula arctica). Biochem. Pharmacol. 26: 1000-1001, 1977.

Guarino, A.M., James, M.O. and Bend, J.R.: Fate and distribution of the herbicides 2,4-dichlorophenoxyacetics acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in the dogfish shark. Xenobiotica 7: 623-632, 1977.

James, M.O. and Bend J.R.: A radiochemical assay for glycine N-acyltransferase activity: Some properties of the enzyme in rat and rabbit. Biochem. J. 172: 285-291, 1978.

James, M.O. and Bend, J.R.: Perinatal development of, and effect of chemical pretreatment on, glycine N-acyltransferase activities in liver and kidney of rabbit and rat. Biochem. J. 172: 293-299, 1978.

Mukhtar, H. and Bend, J.R.: Serum glutathione S-transferases: Perinatal development, sex difference, and effect of carbon tetrachloride administration on enzyme activity in the rat. Life Sci. 21: 1277-1286, 1977.

Smith, B.R., Philpot, R.M. and Bend, J.R.: Metabolism of benzo(a)pyrene by the isolated, perfused rabbit lung. Drug Metab. Disp. 6: 425-431, 1978.

Mukhtar, H., Lee, I.P., Foureman, G.L. and Bend, J.R.: Epoxide-metabolizing enzyme activities in rat testes: Postnatal development and relative activity in interstitial and spermatogenic cell compartments. Chem.-Biol. Interact. 22: 153-165, 1978.

Bornstein, W.A., Chuang, H., Bresnick, E., Mukhtar, H. and Bend, J.R.: Epoxide hydrase activity in liver nuclei: Hydration of benzo(a)pyrene 4,5-oxide and styrene oxide. Chem.-Biol. Interact. 21: 343-346, 1978.

Mukhtar, H., Philpot, R.M. and Bend. J.R.: Epoxide-metabolizing enzyme activities and cytochrome P-450 content of rat ovaries during pregnancy. Biochem. Biophys. Res. Commun. 81: 89-98, 1978.

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Bend, J.R.: Peroxide as a co-factor for oxidation of arachidonic acid by cytochrome P450: Potentia role in oxidant stress-mediated pathology. Invited presentation at Winter Eicosanoid Conference, Baltimore, MD, March 7-10, 1999.

Bend, J.R. Organized an invited symposium for the American Society of Pharmacology and Therapeutics on Cytochrome P450 and chemical toxicity in the respiratory tract. Experimental Biology Meeting, Washington, DC, April 18, 1999; and presented "Oxidant stress mediated formation of bilirubin, an endogenous Ah receptor ligand, as an inductive mechanism for pulmonary CYP1A1 in pathobiology.

BOOK CHAPTERS/REVIEW ARTICLES

Bend, J.R. and Hook, G.E.R.: Hepatic and extrahepatic mixed-function oxidases. In Lee, D.H.K. (Ed.): Handbook of Physiology, Section 9 - Reactions to Environmental Agents. Washington, D.C., American Physiological Society, 1977, pp. 419-440.

Jerina, D.M. and Bend, J.R.: Glutathione S-transferases. In Jollow, D., Kocsis, J.J., Snyder, J. and Vainio, H. (Eds.): Biological Reactive Metabolites. New York, Plenum Press, 1977, pp. 207-230.

Bend, J.R. and James, M.O.: Xenobiotic metabolism in freshwater and marine species. In Malins, D.C. and Sargent, J.R. (Eds.): Biochemical and Biophysical Perspectives in Marine Biology, Vol. 4. New York, Academic Press, 1978, pp. 125-188.

Bend, J.R., James, M.O. and Pritchard, J.B.: Aquatic toxicology. In Guthrie, F.E. and Perry, T.O. (Eds.): Introduction to Environmental Toxicology. New York, Elsevier/North Holland, 1980, pp. 172-185.

Smith, B.R. and Bend, J.R.: Lung perfusion techniques for xenobiotic metabolism an toxicity studies. In Jakoby, W.B. (Ed.): Methods in Enzymology, Vol. 77 Detoxication and Drug Metabolism: Conjugation and Related Systems. New York, Academic Press, 1981, pp. 105-120.

Plummer, J.L., Smith, B.R., Sies, H. and Bend, J.R.: Glutathione depleting and oxidizing agents. In Jakoby, W.B. (Ed.): Methods in Enzymology, Vol. 77. Detoxication and Drug Metabolism: Conjugation and Related Systems. New York, Academic Press, 1981, pp. 50-59.

Smith, B.R. and Bend, J.R.: Metabolic interactions of hydrocarbons with mammalian lung. In Hodgson, E., Bend, J.R. and Philpot, R.M. (Eds.): Reviews in Biochemical Toxicology, Vol. 3. New York, Elsevier/North Holland, 1981, pp. 77-122.

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Bend, J.R. and Serabjit-Singh, C.J.: Xenobiotic metabolism by extrahepatic tissues: Relationship to target organ and cell toxicity. In Mitchell, J.R. and Horning, M.G. (Eds.): Drug Metabolism and Drug Toxicity, New York, Raven Press, 1984, pp. 99-136.

Bend, J.R., Serabjit-Singh, C.J. and Philpot, R.M.: Pulmonary uptake, accumulation and metabolism of chemicals. Ann. Rev. Pharmacol. Toxicol. 25: 97-125, 1985.

Bend, J.R. and Muller, D.: Metabolism. In: Environmental Health Criteria 57. Principles of Toxicokinetic Studies. Geneva World Health Organization, 1986, pp. 45-81.

Bend, J.R.: Estimation of induction of enzymes that metabolize xenobiotics *in vitro* and *in vivo*. In Contaminants and the Environment: A Multidisciplinary Assessment of Risks to Man and Other Organisms, A. Renzoni, N. Mattei, L. Lari and M.C. Fossi, Eds., Lewis Publishers, pp. 93-101, 1994.

Bend, J.R. and Karmazyn, M. Role of eicosanoids in ischemic and reperfused myocardium. In Karmazyn, M. (Ed.): Myocardial Ischemia: Mechanisms, Reperfusion, Protection. Birkhauser Verlag AG, Boston, USA, 1996, pp. 243-262.

Karmazyn, M. and Bend, J.R.: Biochemical and molecular mechanisms of myocardial injury. In Comprehensive Toxicology, series edited by Sipes, G., McQueen, C.A. and Gandilfi, A.J.; Volume 6. Cardiovascular Toxicology, edited by Bishop, S.P., Elsevier-Pergamon Publishers, 1997, pp.255-278.

Sinal, C.J. and Bend, J.R. Hormesis. In Wexler, P. (Ed.): Encyclopedia of Toxicology, Vol. 2. (*F-P*), Academic Press, New York, USA, 1998, pp. 88-92.

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Lui, E.M.K., Suzuki, C. and Bend, J.R. Information Resources in Toxicology, Canada. In Wexler, P. (Editor-in-Chief.): *Information Resources in Toxicology*, Third Edition. Academic Press, New York, USA, 2000, pp. 583-598.

Rapport, D.J., Howard, J., Lannigan, R., McMurtry, R.Y., Jones, D.L., Anjema, C.M. and Bend, J.R. Thinking outside the box: Introducing ecosystem health into undergraduate medical education. In: Section 4: Challenges Ahead for Implementing Conservation Medicine. Invited Chapter in *Conservation Medicine: Ecological Health in Practice*. Oxford University Press, 2002, pp. 345-360.

Kroes, R., DiNovi, M. and Bend, J.R. Benzoyl Peroxide. (First draft). In WHO FOOD ADDITIVES SERIES: 54 Safety evaluation of certain food additives. Prepared by the Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). International Programme on Chemical Safety, World Health Organization, Geneva, 2006 pp 11-35.

Pronk, M.E.J. and Bend, J.R. Aliphatic and Alicyclic Hydrocarbons (First draft). In WHO FOOD ADDITIVES SERIES: 54 Safety evaluation of certain food additives. Prepared by the Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). International Programme on Chemical Safety, World Health Organization, Geneva, 2006 pp 235-289.

Pronk, M.E.J. and Bend, J.R. Aromatic Hydrcarbons (First draft). In WHO FOOD ADDITIVES SERIES: 54 Safety evaluation of certain food additives. Prepared by the Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). International Programme on Chemical Safety, World Health Organization, Geneva, 2006 pp 291-316.

Williams, G.M. and Bend, J.R. Aliphatic, Linear α,β-Unstaurated Aldehydes, Acids and Related Alcohols,Acetals and Esters (First draft). In WHO FOOD ADDITIVES SERIES: 54 Safety evaluation of certain food additives. Prepared by the Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). International Programme on Chemical Safety, World Health Organization, Geneva, 2006 pp 317-383.

Benford, D., Street, D.A., Leclerq, C. and Bend, J.R. Report Topic Aluminium (all sources, including food additives). 67th Report of the Joint FAO-WHO Expert Committee on Food Additives (JECFA), Rome, June 20-29, 2006 (In press).

GOVERNMENT REPORTS

Bend, J.R., Corbett, B.A., Darnell, R., Herbert, C.P., Koren, G., Kowal, N., Rieder, M.J., Stephens, C. and Trick , C.G. (UWO) and Harrison, L., Peters, J. and White, D. (Walpole Island First Nation): Feasibility of Conducting Epidemiological Studies to Assess the Health Risk of the Walpole Island First Nation Community from Exposure to Environmental Contaminants. 82 pp, May 31, 2005; Report to Health Canada and the Walpole Island First Nation..

Bend, J.R., Darnell, R., Herbert, C.P., Kowal, N., Trick, C.G. (UWO) and Williams, N. and White, D. (Walpole Island First Nation): Walpole Island First Nation Mercury Exposure through Fish Consumption Study, 2005/2006, 41 pp., August 31, 2006; Report to Health Canada and the Walpole Island First Nation.

EDITING

de Serres, F.J., Fouts, J.R., Bend, J.R. and Philpot, R.M.: In Vitro Metabolic Activation in Mutagenesis Testing. New York, Elsevier/North Holland, 1976, 363pp.

Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 1. New York, Elsevier/North Holland, 1979, 316 pp.

Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 2. New York, Elsevier/North Holland, 1980, 300 pp.

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Jakoby, W.B., Bend, J.R. and Caldwell, J.: Metabolic Basis of Detoxication. New York, Academic Press, 1982, 375 pp.

Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 5. New York, Elsevier Biomedical, 1983, 415 pp.

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Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 7. New York, Elsevier Biomedical, 1985, 287 pp.

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Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 9. New York, Elsevier, 1988, 347 pp.

Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 10, New York, Elsevier, 1989, 393 pp.

Hodgson, E., Bend, J.R. and Philpot, R.M.: Reviews in Biochemical Toxicology, Vol. 11, Toxicology Communications, 1995, 222 pages.

Bend, J.R. and Hodgson, E. Section Editors, Biochemical Toxicology in Reviews in Toxicology, E. Hodgson, Editor. Vol. 1, 1997, 156 pages.

PATENT

Hernandez, O., Bend, J.R., Eling, T.E. and McKinney, J.D.: Synthesis of optically pure thromboxanes. U.S. Patent No. 4,256,646. March 17, 1981.

BOOK REVIEW

Bend, J.R.: Animals as monitors of environmental pollutants. Environ. Research 24: 229-231, 1981.

INVITED ORAL PRESENTATIONS

Fouts, J.R., Bend, J.R., James, M.O. and Devereux, T.R.: Perinatal development of N-oxidase, N-demethylase, epoxide hydrase and glutathione (GSH) S-epoxide transferase in hepatic and extrahepatic tissues of guinea pigs and rabbits. International Symposium on Perinatal Pharmacology, Milan, Italy, June 13-15, 1974.

Bend, J.R.: In vitro metabolism of xenobiotics by selected marine species. Interagency Collaborative Group on Environmental Carcinogenesis, September 18, 1974 (Washington, D.C., National Library of Medicine).

Bend, J.R.: Seminar entitled "Pulmonary Metabolism of Xenobiotics". School of Medicine, University of Pennsylvania, January 28, 1975.

Bend, J.R.: Research proposed by the National Institute of Environmental Health Sciences to study the effect of the respiratory irritation associated with Florida Red Tide on human health. Flor. Mar. Res. Publ. 8: 14, 1975.

Bend, J.R.: Pulmonary metabolism of xenobiotics. Presented at a Symposium entitled "Some Newer Developments in Respiratory Toxicology". 14th Annual Meeting of the Society of Toxicology, Williamsburg, Virginia, March 11, 1975.

Bend, J.R., Hart, L.G., Guarino, A.M., Rall, D.P. and Fouts, J.R.: Distribution and excretion of ^{14}C-2,4,5,2',5'-pentachlorobipheryl in the dogfish shark and the lobster. National Conference on Polychlorinated Biphenyls, Chicago, Illinois, November 19-21, 1975.

Bend, J.R.: Effects of inducers on the in vitro metabolic activation system used in mutagenesis testing with the Ames Test. In vitro Metabolic Activation Conference, Research Triangle Park, N.C., Feb. 9-11, 1976.

Bend, J.R., James, M.O., Ben-Zvi, Z., Law, F.C.P. and Ryan, A.J.: Hepatic and extrahepatic metabolism of ^{14}C-styrene oxide. Presented at the WHO-NIEHS Symposium on Potential Health HAzards from Technological Development in the Rubber and Plastic Industries. Research Triangle Park, N.C., March 1-3, 1976.

Bend, J.R., James, M.O., Pohl, R.J. and Fouts, J.R.: Xenobiotic metabolism by marine vertebrate and invertebrate species form Maine and Florida. Presented at the Biological Effects Program Workshop, National Science Foundation International Decade of Ocean Exploration (IDOE) Program, Texas A and M University, May 16-19, 1976.

James, M.O., Fouts, J.R. and Bend, J.R.: Xenobiotic metabolizing enzymes in marine fish. Symposium on Pesticides in the Aquatic Environment, XV International congress of Entomology, Washington, D.C., August, 1976.

Philpot, R.M., James, M.O. and Bend, J.R.: Metabolism of benzo(a)pyrene and other xenobiotics by microsomal mixed-function oxidases in marine species. Symposium on "Sources, Effects and Sinks of Petroleum in the Aquatic Environment". Am. Inst. Biol. Sciences Symposium, Washington, D.C., August, 1976.

Bend, J.R.: Metabolism of epoxides by epoxide hydrase and glutathione S-transferases. Symposium entitled "Formation of Chemically Reactive Metabolites as a Cause of Drug Toxicity". Sponsored by Drug Metabolism Division of the American Society for Pharmacology and Experimental Therapeutics. New Orleans, La., August, 1976.

Bend, J.R., James, M.O. and Dansette, P.M.: In vitro metabolism of xenobiotics in some marine animals. Conference on "Aquatic Pollutants and Biological Effects with Emphasis on Neoplasia". New York Academy of Sciences. New York Academy of Sciences, New York, N.Y., September, 1976.

Bend, J.R.,: Xenobiotic metabolism. Conference entitled "Status of Predictive Tools in Application to Safety Evaluation: Present and Future". Sponsored by NIH and NCTR, Little Rock, Arkansas, November, 1976.

Bend, J.R.: Metabolism of xenobiotics by marine species. Seminar presented at the Department of Pharmacology, Medical College, Milwaukee, Wisc., December, 1976.

Bend, J.R.: Metabolic reactions in vivo and in vitro. Toxicology forum on "Short Term Tests for Carcinogenicity". Hunt Valley, Maryland, February 7-9, 1977.

Bend, J.R.: In vitro and in vivo metabolism of xenobiotics by marine species of coastal Maine and Florida. EPA Energy/Marine Fate and Effects Conference, Newport, Rhode Island, March 1-3, 1977.

Bend, J.R., Foureman, G.L. and James, M.O.: Presented a paper entitled "Partially Induced Hepatic Mixed-Function Oxidase Systems in Individual Members of Certain Marine Species form Coastal Maine and Florida" at the Second International Symposium on Aquatic Pollutants, September 27, 1977, Amsterdam, Teh Netherlands.

Bend, J.R., Smith, B.R., Van Anda, J., Ryan, A.J. and Fouts, J.R.: Biotransformation of epoxides by isolate,d perfused liver and lung preparations versus subfractions of homogenized liver and lung cells. International Conference on "In Vivo Aspects of Biotransformation and Toxicity of Industrial and Environmental Xenobiotics", Czechoslovakia, September 12-15, 1977.

James, M.O. and Bend, J.R.: Xenobiotic metabolism in marine species exposed to hydrocarbons. Second National Conference on Interagency Energy/Environment Research and Development Programs, Washington, D.C., June 5-6, 1977.

Bend, J.R.: Invited lecturer at the NATO Conference on Ecotoxicology, University of Surrey. "The Effects of environmental chemicals on marine species and the effects of marine species on environmental chemicals", Guildford,, U.K., July 21, 1977.

Bend, J.R.: Presented a paper entitled "Pulmonary Metabolism of Epoxides" at a Symposium on Environmental Pharmacology of the Lung, ASPET Meeting, Columbus, Ohio, August, 1977.

Smith, B.R. and Bend, J.R.: Presented a paper entitled "Metabolism of Benzo(a)pyrene 4,5-Oxide by the Isolate Perfused Rabbit Lung" ar the Second International Symposium on Polynuclear Aromatic Hydrocarbons, Columbus, Ohio, September 29, 1977.

Bend, J.R.: Lecture on "Aquatic Toxicology" given as part Environmental Toxicology course ar N.C. State University, Raleigh, N.C., April 4, 1978.

James, M.O. and Bend, J.R.: Effect of polynuclear aromatic hydrocarbons and polyhalogenated biphenyls on hepatic mixed-function oxidase activity in marine fish. Symposium on "Carcinogenic Polynuclear Aromatic Hydrocarbons in the Marine Environment", U.S. Environmental Protection Agency, Pensacola Beach, Florida, August 14-18, 1978.

Bend, J.R.: Presentation entitled "Glutathione S-transferases--Catalytic Aspects" given at Gordon Conference on Drug Metabolism, Plymouth, N.H., August 9, 1978.

Bend, J.R.: Seminar entitled "Xenobiotic Biotransformation in Aquatic Species" presented at Mount Desert Island Biological Laboratory, Salsbury Cove, Maine, August 24, 1978.

Bend, J.R.: Invited speaker at Sympodium on "Metabolism and Disposition of Pesticides and Other Chemicals in Aquatic Organisms". 176th Meeting of the American Chemical Society, Miami Beach, Florida, September 13-14, 1978.

Bend, J.R.: Chairman, Session on "Pharmacological Modulation". Symposium on "Host Defense Mechanisms in the Respiratory Tract".

Bend, J.R.: Seminar entitled "Hepatic and Extrahepatic Metabolism of Alkene and Arene Oxidase". Presented at Department of Pharmacology , University of Minnesota, Minneapolis (December, 1978) and Department of Biochemistry, McMaster Medical School, Hamilton, Ontario, January, 1979.

Bend, J.R.: Seminar entitled "Aquatic Biomedicine Program of the National Institute of Environmental Health Sciences" at EPA Water Control Laboratory, Duluth, MN, December, 1978.

Bend, J.R.: Invited speaker at workshop on "PCBs in the Marine Environment". Organized by FDA for Mid-Atlantic Fishery Management Council, Cape May, N.J., May, 1979.

Bend, J.R.: Lecturer (2 hours) on "Metabolic Activation and Detoxification of Environmental Pollutants by Marine Vertebrate and Invertebrate Species" as part of Biology 3420. Seminar in Environmental Science ar North Carolina Central University, Durham, N.C., October 18, 1979.

Bend, J.R.: Seminar on "Integrated Pulmonary Systems for the Study of Xenobiotic Metabolism and Toxicity" given ar ICI, Aldersley, U.K., October 21, 1979.

Bend, J.R.: Invited speaker at Ciba Foundation Symposium on :Drug Metabolizing Enzymes and Environmental Chemicals: Toxic Interactions". Title of presentation was "Induction of Drug-Metabolizing Enzymes by Polycyclic Aromatic Hydrocarbons: Mechanisms and Some Implications in Environmental Research. London, October 23-25, 1979..

Bend, J.R.: Seminar entitled "Mechanisms of Polycyclic Hydrocarbon Induction of the Hepatic Monooxygenase System and Heterogeneity of Benzo(a)pyrene Hydroxylase Activity in Teleost Fish form Maine" presented to the Toxicology Program ar the University of Arizona, November 13, 1979.

Bend, J.R.: Graduate lecture given to pharmacology and toxicology students of University of Arizona on "Comparative Aspects of Glutathione Conjugation", November 14, 1979.

Bend, J.R.: Seminar entitled "Integrated Pulmonary Systems for the Study of Xenobiotic Metabolism and Toxicity", Department of Pharmacology, University of Arizona, November 14, 1979.

Bend, J.R.: Seminar on "Drug Metabolism and Toxicity in Integrated Pulmonary Biotransformation Systems", Departments of Pharmacology, Biochemical Pharmacology and Toxicology, University of Utah, November 15, 1979.

Bend, J.R.: Graduate lecture (2 hours) given to pharmacology and toxicology student on "Comparative Aspects of Enzyme Induction and Glutathione Conjugation", University of Utah, November 16, 1979.

Bend, J.R.: Invited speaker at a Drug Metabolism Symposium sponsored by the Drug metabolism Discussion Group[(topic was "Epoxide Metabolism"). Fort Washington, Pennsylvania, May 7-9, 1980.

Bend, J.R.: Invited speaker at the 10th International Linderstrom-lang Conference on "Conjugation Reactions in Drug and Carcinogen Metabolism", Skokloster, Sweden, June 22-25, 1980.

Bend, J.R.: Invited speaker at the Second International Congress of Toxicology Satellite Symposium on "Freshly Isolated Cells form Adult Animals: Use in Biochemical Toxicology", Leuven, Belgium, July 12-13, 1980.

Bend, J.R.: Invited speaker at the Second International Symposium on "Biological Reactive Intermediates", Guildford, U.K., July 14-17, 1980.

Bend, J.R.: Invited speaker at an International Conference on "Veterinary Pharmacology, Toxicology and Therapeutics", Cambridge, U.K., July 28 - August 1, 1980.

Bend, J.R.: Invited speaker ar the 11th International Princess Takamatsu Cancer Symposium on "Phyletic Approaches to Cancer", Tokyo, Japan, November 11-13, 1980.

Bend, J.R.: Seminar entitled "The Glutathione Transferases: Role in Epoxide Metabolism" given at the Department of Pharmacology, Keio University School of Medicine, Tokyo, Japan, November 14, 1980.

Bend, J.R.: Seminar entitled "Heterogeneity of Monooxygenase Activity on Marine Fish: Evidence for Enzyme Induction in Nature" presented at the Zoological Institute, University of Tokyo, Japan, November 18, 1980.

Bend, J.R.: Invited speaker at an International Symposium on "Organophosphates and the Marine Environment" held at the Duke University Marine Laboratory, Beuford, N.C., June 8-9, 1981.

Bend, J.R.: Presentation entitled "Studies of DNA Adducts of Benzo(a)pyrene Found <u>In Vivo</u> given at the Advisory Subgroups on Toxicology, European Medical Research Councils Meeting on "Estimation of Previous Exposure of Man to Substances Reacting Covalently with Macromolecules", Lyon, France, October 30, 1981.

Bend, J.R.: Seminar entitled "Enzymatic Formation and Degradation of Glutathione Conjugates" presented to the Departments of Dermatology and Pharmacology, Case Western Reserve University, Cleveland, Ohio, November, 18, 1981.

Bend, J.R.: Seminar entitled "Stereoselectivity and Regioselectivity in the Enzymatic Reaction of Model Alkene and Arene Oxides with glutathione" presented to the Departments of Biological Chemistry and Pharmacology, University of Michigan, Ann Arbor, Michigan, November 20, 1981.

Bend, J.R.: Invited speaker ar an International Symposium on "The Use of Small Fish Species in Carcinogenicity Testing" sponsored by the National Cancer Institute and held at the NIH, Bethesda, Maryland, December 8-10, 1981.

Bend, J.R.: Seminar entitled "The Glutathione Transferases - Multiple Functions" presented to the Chemical Carcinogenesis Program, University of North Carolina, Chapel Hill, N.C., February 1, 1982.

Bend, J.R.: Lecture entitled "Embryonic and Fetal Drug Metabolism" given at the University of North Carolina as part of Anatomy 123-Tox C (Developmental Toxicology and Teratology), March 24, 1982.

Bend, J.R.: Lecture entitled " Basic and Applied Toxicology Research at NIEHS" given to the Departments of Biochemistry and Pharmacology, University of Texas Health Science Center, Dallas, April 1, 1982.

Bend, J.R.: Chairman, Session on "Genetic Differences in Carcinogen Metabolism" at the Sixth Annual Symposium of the Cancer Research Center (Symposium title: Genetic Mechanisms in Chemical Carcinogenesis), University of North Carolina, Chapel Hill, N.C., April 6, 1982.

Bend J.R.: Chairman, Session on "Metabolism of Genotoxic Agents in Human Cells and Its Relevance to Risk Assessment" at the American-Swedish workshop on "Individual Susceptibility to Genotoxic Agents in the Human Population", Research Triangle Park, N.C., May 10-12, 1982.

Hernandez, O., Foureman, G.L., Bhatia, A., Walker, M. and Bend, J.R.: Poster presentation entitled " Stereoselectivity in the Enzymatic Reaction of Glutathione with Several K-region Polycyclic Arene Oxides" given at the Fifth Karolinska Institute Nobel Conference on "Functions of Glutathione--Biochemical,Physiological and Toxicological Aspects", Skokloster, Sweden, May 24, 1982.

Harris, C., Hernandez, O., Bhatia, A., Yagen, B. and Bend, J.R.: Poster presentation entitled "Stereoselectivity of Rat Liver Glutathione Transferases with Styrene 7,8-Oxide as Substrate" given at the Fifth Karolinska Institute Nobel Conference, Skokloster, Sweden, May 25, 1982.

Bend, J.R.: Paper entitled "Metabolism of 2-Acetylaminofluorene by Rabbit Lung to Mutagenic Products" presented at a Minisymposium on "Drug Metabolism", Department of Forensic Medicine, Karolinska Institute, Stockholm, Sweden, May 27, 1982.

Bend, J.R.: Presentation entitled "Variability of Certain Hepatic Monooxygenase Activities in Feral Winter Flounder (Pseudopleuronectes americanus) form Maine: Apparent Association with Induction by Environmental Exposure to PAH-type Compounds" given at the Fourth International Conference on Cytochrome P-450: Biochemistry, Biophysics and Environmental Implications", Kuopio, Finland, May 31 - June 3, 1982.

Bend, J.R.: Seminar entitled "Metabolism of 2-Acetylaminofluorene by Rabbit Lung: Correlation with the Formation of Mutagenic Products" presented at the Institute for Occupational Health, Helsinki, Finland, June 4, 1982.
Bend, J.R.: Presented an NIH Intramural Scientific Research Seminar entitled "An Integrated Approach for Studying the Relationship Between Metabolism and Toxicity in Hepatic and Extrahepatic Tissues", October 15, 1982.

Bend, J.R.: Seminar entitled "An Integrated Approach for Studying the Relationship Between Metabolism and Toxicity in Target Organs or Cells", Faculty of Pharmacy, University of Toronto, December 7, 1982.

Bend, J.R.: Seminar entitled "Metabolism of Benzo(a)pyrene: Formation and Disappearance of Benzo(a)pyrene-DNA Adducts in Mammalian Lung" presented to the Department of Pharmacology, Toxicology and Biochemistry, Medical College of Wisconsin, Milwaukee, December 10, 1982.

Bend, J.R.: Invited speaker at the Second International Symposium on "Responses of Marine Organisms to Pollutants" held in Woods Hole, Massachusetts, April 27-29, 1983.

Bend, J.R.: Presentation entitled "In vivo Metabolism of Benzo(a)pyrene: Formation and Disappearance of BP Metabolite-DNA Adducts in Extrahepatic Tissues Versus Liver" at an International Symposium entitled "Extrahepatic Drug Metabolism and Chemical Carcinogenesis", Stockholm, Sweden, May 17-20, 1983.

Bend, J.R.: Presentation entitled "Stereoselectivity of Glutathione Transferases with Model Alkene and Arene Oxides" at a Symposium on "Metabolism and Chemical Carcinogenesis", Oslo, Norway, May 24, 1983.

Bend, J.R.: Presentation entitled "Relationships Between Xenobiotic Metabolism and Target Cell Toxicity in the Lung" at the Second Annual Colloquium of the New Jersey Joint Program in Toxicology on "Lung Toxicity: Mechanisms and Biological Consequences", Piscatway, New Jersey, June 3-4, 1983.

Bend, J.R: Seminar titled "Stereoselectivity in the Metabolism of Styrene" presented to the Department of Biochemistry and the Program in Toxicology, Vanderbilt University, February 13, 1984.

Bend, J.R.: Presentation titled "Xenobiotic Metabolism in Lung: Relationship to Target Organ and Cell Toxicity" presented to the Delaware Valley Drug Metabolism Discussion Group, Plymouth Meeting, PA, March 21, 1984.

Bend, J.R.: Seminar titled "Chemical Metabolism by Lung: Importance in Target Organ and Cell Toxicity" presented at Canadian Centre for Toxicology, University of Guelph, Guelph, Canada, September 14, 1984.

Bend, J.R.: Seminar titled" Stereoselectivity in the Formation and Metabolism of Epoxides" in the Faculty of Pharmacy, University of British Columbia, November, 1984. (Given as part of duties of Medical Research Council of Canada Visiting Professor.)

Bend, J.R.: Presentation titled "Comparative Biochemistry of the Lung: Importance of Cellular Heterogeneity" given at the Symposium on Problems of Drug-Related Damage to the Respiratory System, West Berlin, Germany, February 25-28, 1985.

Bend, J.R.: Seminar titled "Stereoselectivity in the Cytochrome P-450-Dependent Formation and Subsequent Metabolism of Styrene 7,8-Oxide" presented at the Institute for Toxicology, University of Mainz, March 1, 1985.

Bend, J.R.: Presentation titled "Xenobiotic Metabolism by the Perfused Lung" at a Symposium on the lung at the Fall meeting of the Norwegian Society of Pharmacology and Toxicology, September 16, 1985, Oslo.

Bend, J.R.: Seminar titled "Drug Metabolism, An Important Non-Respiratory Function of Lung" given at the Department of Pharmacology, University of Western Ontario, London, Canada on July 2, 1986.

Bend, J.R.: Presentation titled "Drug-Induced Lung Toxicity: Effect of Lung on Metabolism and Disposition of Drugs" given in the plenary session of a FASEB-sponsored conference on "Lung Pharmacology and Pathophysiology", July 27 - August 1, 1986, Vermont Academy, Saxton's River, Vermont.

Bend, J.R.: Seminar titled "Isozyme selective suicide substrates of cytochrome P-450" given to the Department of Pharmacology and Toxicology, University of Western Ontario, London on February 27, 1987.

Bend, J.R.: Seminar titled "Isozyme selective suicide substrates for cytochrome P-450 in lung" given to the Department of Pharmacology and Toxicology, Queen's University, Kingston, Ontario on March 10, 1987.

Bend, J.R.: Seminar titled "Mechanisms for xenobiotic-mediated target organ toxicity in lung" given to the Department of Pathology, University of Western Ontario, London on March 20, 1987.

Bend, J.R.: Seminar titled "The glutathione S-transferases - an important family of enzymes for the metabolism of endogenous chemicals" given at the St. Joseph's Research Institute, University of Western Ontario on March 31, 1987.

Bend, J.R.: Seminar titled "Mechanism-based isozyme selective inhibitors of cytochrome P-450" given to the Department of Biochemistry, University of Guelph, Guelph, Ontario on April 8, 1987.

Bend, J.R.: Department of Environmental Biology, University of Siena, Italy, "Heterogeneity of cytochrome P-450-dependent aryl hydrocarbon hydroxylase activity in Pseudopleuronectes americanus (winter flounder); evidence for enzyme induction in fish of coastal Maine", July 7, 1987.

Bend, J.R.: Departments of Pharmacology and Environmental Biology, University of Siena, Italy, "Isozyme selective mechanism-based (suicide) inhibitors of the cytochrome P-450 monooxygenase system", July 8, 1987.

Bend, J.R.: Department of Toxicology, University of Leiden, The Netherlands, "Isozyme selective suicide substrates for pulmonary cytochrome P-450", Aug. 31, 1987.

Bend. J.R.: Invited Speaker at a Symposium on Organ Perfusion Systems in Drug Disposition Studies, 47th International Congress of Pharmaceutical Sciences, Amsterdam, Aug. 31 - Sept. 4, 1987.

Bend, J.R.: Invited Speaker at Summer School of Multidisciplinary Assessment of Environmental Risks for Human Health, University of Siena, Sept. 9-15, 1987. Presentation was titled "Estimation of induction of enzymes that metabolize xenobiotics in vitro and in vivo".

Bend, J.R.: Department of Fisheries and Oceans, Government of Canada, Workshop on Long Range Transport of Atmospheric Pollutants (LRTAP). Made presentation title, "Induction of the hepatic microsomal cytochrome P-450 monooxygenase system in fish by polycyclic aromatic hydrocarbon-type compounds as a sensitive endpoint for bioeffects monitoring", Burlington, Ontario, Oct. 14-15, 1987.

Bend, J.R.: Department of Pharmacology, Dalhousie university, "Isozyme selective - mechanism based inhibitors of pulmonary cytochrome P-450", Nov 24, 1987.

Bend, J.R.: Department of Pharmacology, University of Toronto, "Isozyme selective, mechanism-based inhibitors of cytochrome P-450", Jan. 19, 1988.

Bend J.R.: Department of Pharmacology and Therapeutics, McGill University, "Isozyme selective, mechanism-based inhibitors of cytochrome P-450", Feb. 9, 1988.

Bend, J.R.: UWO Pulmonary Interhospital Group, UWO; "Pulmonary cytochrome P-450 system: selective modulation of isozymes by mechanism-based inhibitors", March 23, 1988.

Bend, J.R.: Alberta Heritage Foundation for Medical Research, Guest Speaker, University of Alberta, March 8, 1989; "Isozyme selective mechanism - based inhibitors of cytochrome P-450".

Bend, J.R.: Albera Heritage Foundation for Medical Research, Guest Speaker, University of Alberta, March 9, 1989; "Cell selective toxicity in the lung: role of pulmonary metabolism".

Bend, J.R.: Fifth International Congress of Toxicology, Brighton, England, Invited speaker, July 16-21, 1989; "Cell selective toxicity of xenobiotics in the lung: role of metabolism".

Bend, J.R.: Fourth Annual Toxicology Symposium, University of Guelph, Invited speaker, February 10, 1990.

Bend, J.R.: Biochemistry Department, Memorial University of Newfoundland, St. John's, Invited speaker, March 16, 1990; "Isozyme selective, tissue selective mechanism-based inhibitors of cytochrome P-450".

Bend, J.R.: Department of Physiology, University of Western Ontario, Invited speaker, April 2, 1990; "Cytochrome P-450-dependent metabolism of arachidonic acid: utility of mechanism-based inhibitors for studies of biological significance".

Bend, J.R.: Department of Pathology, University of Toronto, Invited speaker, May 16, 1990; "Correlation between chemical metabolism and target organ xenobiotic toxicity in lung".

Bend, J.R.: Department of Pharmacology and Toxicology, Queen's University, Invited Speaker, Aug. 2, 1990. "Mechanism-based inhibitors of cytochrome selective for the lung".

Bend, J.R.: Department of Pharmacology, University of Toronto, Invited Speaker, May 1, 1991. "Isozyme selective metabolism of arachidonic acid by microsomal cytochromes P450 in the guinea pig".

Bend, J.R.: Department of Biochemistry, University of Western Ontario, Invited Speaker, September 27, 1991. "Isozyme selective, tissue selective mechanism-based inhibitors of cytochrome P450".

Bend,J.R. (invited speaker), Knickle, L.C., Webb, C.D. and Woodcroft, K.J.: Isozyme selective mechanism-based inhibitors of pulmonary cytochrome P450 (Symposium, US Society of Toxicology). Toxicologist 13: 15, 1993.

Bend, J.R.: Vascular Biology Group, Victoria Hospital, London, Ontario. Invited Speaker May 4, 1993. "Cytochrome P450 and nitric oxide synthase".

Bend, J.R.: Environmental Health Directorate Seminar Series, Banting Research Centre, Tunney's Pasture, Ottawa, Ontario, February 8, 1994. "Environmental modulation of enzyme systems important in bioactivation of exogenous and endogenous chemicals".

Bend, J.R.: Environmetrics Colloquium, Department of Applied Mathematics, University of Western Ontario, October 26, 1994. Seminar titled "Biomarkers and Environmental Contaminants".

Bend, J.R.: Cytochrome P450 and arachidonic acid bioactivation. Heritage Visiting Professor, University of Calgary, March 1, 1996.

Bend, J.R.: Seminar at Department of Pharmacology, University of Michigan, Ann Arbor, "Bilirubin but not Heme or Bilinerdin is an Endogenous Aryl Hydrocarbon Receptor Ligand." April, 1996.

Bend, J.R.: Invited speaker to the 25th Anniversary of the Department of Pharmacology and Toxicology, Centro De Investigacion Y Estudios Avanzados IPN, Mexico City along with Professors John C. McGiff (New York Medical College) and Sir John Vane (William Harvey Institute). Talk was titled "Inhibitory effect of cytochrome P450 3A and 1A isozymes by grapefruit juice". August 2, 1996.

Bend,J.R.: Invited to organize symposium on "Drug-drug and drug-chemical interactions based on modulation of cytochrome P450 1A and 3A subfamilies" for the VIth World Congress on Clinical Pharmacology and Therapeutics, Buenos Aires, August 4-10, 1996.

Bailey, D.G., Rau, S.E., Munoz, C., Ito, S., Tesoro, A., Freeman, D.J., Spence, J.D. and Bend, J.R.: Inhibition of CYP3A and CYP1A isozymes by grapefruit juice and grapefruit juice constituents *in vivo* and *in vitro*. In Symposium titled: Drug-drug and drug-chemical interactions based on modulation of monooxygenase activities catalyzed by cytochrome P450 1A and 3A subfamilies. VI World Conference on Clinical Pharmacology, Buenos Aires, August, 1996. (Presented by J.R. Bend)

Bend, J.R. Seminar at Department of Pharmacology, New York College of Medicine, Valhalla, New York. "Effects of induction of cytochrome P450 isozymes on arachidonic and metabolism in liver and extrahepatic tissues of guinea pigs." March, 1997.

Bend, J.R. "Symposium on Cytochrome P4503A Isozymes in Humans", organized by invitation for Western Society of Pharmacology meeting in Mazatlan, Mexico, Jan. 25-29, 1998.

Bend, J.R: Peroxide as a co-factor for oxidation of arachidonic acid by cytochrome P450: Potential role in oxidant stress-mediated pathology. Invited presentation at Winter Eicosanoid Conference, 1999, Baltimore, MD, March 7-10.

Bend, J.R.: Organized an invited symposium for the American Society of Pharmacology and Toxicology (ASPET) on Cytochrome P450 and chemical toxicity in the respiratory tract, Experimental Biology Meeting, Washington, DC, April 18, 1999. Will present one of the four talks in this symposium, titled Oxidant stress mediated formation of bilirubin, an endogenous Ah receptor ligand, as an inductive mechanism for pulmonary CYP1A1 in pathobiology.

Bend, J.R.: Moderstor and Co-organizer (with Dr. Heather Durham, President Society of Toxicology of Canada (STC) of the session, Emerging Opportunities for Collaboration and Funding in in Toxicology. Held at the 34th Annual Symposium of the STC, December 6-7, 2001, Montreal, Quebec..

Bend, J.R. : Invited speaker at the European Association for the Study of the Liver (EASL) Workshop on the Molecular Basis of Bilirubin Encephalopathy and Neurotoxicity: The 4th Trieste International Bilirubin Workshop, October 1-2, 2004, Trieste, Italy. The subject of my presentation was: Unconjugated bilirubin as a prooxidant and potentia ligand of the aryl hydrocarbon receptor.

Yaghi, A., Bend, J.R., Zeldin, D.C., Mehta, S. and McCormack, D.G.: Mechanisms of depressed pulmonary artery contractility in a rat model of acute Pseudomonas pneumonia. .Invited oral presentation: Merck Frosst Pharmacology Research Day, Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec (October 22, 2004).

Bend, J.R.: Presentation titled "The CIHR Steering Committee for Health and the Environment", at CIHR Workshop on Reproductive and Developmental Toxicology Researcgh, McGill University, Montreal, Dec. 4-5, 2004. Co-applicant on the CIHR grant that financed this workshop with Barbara Hales (PI; McGill), Bruce Murphy (U Montreal) and Gideon Koren (U Toronto).

Bend, J.R.: Moderator, "An Open Forum Discussion on the Canadian Role in Identifying, Characterizing and Addressing Environmental Health Issues on a Local and Global Scale",. Speakers included: James Bus (Dow Chemical Corporation; Michael Gilbertson, formerly with the International Joint Commission of the Great Lakes; Steve Clarkson, Director of the Environmental Contaminants Bureau, Health Canada; and John Arsenault, Director, Environment Canada. 37th Annual Symposium of the Society of Toxicology of Canada, Montreal, December 6-7, 2004.

Bend, J.R. Invited speaker and guest to the 3rd Meeting of the Consortium for the Globalization of Chinese Medicine (CGCM) held January 29-31, 2005 in Hong Kong. Based on my presentation Western was invited to become the first Canadian member of the Consortium which has more than 30 members from China, Hong Kong, Taiwan and the USA.

Bend, J.R.: Invited seminar titled "Protein Reactive Cysteine Thiols, the Disulfide Proteome, Bilirubin Toxicity and Adverse Drug Reactions" at the National Institute of Environmental Health Sciences/NIH, Research Triangle Park, NC, USA, April 21, 2005.

Bend, J.R.: Invited seminar titled "Proteomics in Molecular Toxicology: Protein Reactive Cysteine Thiols, the Disulfide Proteome and Redox Regulation" at the Robarts Research Institute, London, November 25, 2005.

Bend, J.R: Invited speaker, Paediatrics Grand Rounds, University of Western Ontario. "Bilirubin Toxicity, Oxidative Stress, Redox Regulation and the Disulfide Proteome", January 18, 2006.

Bend, J.R: Invited speaker, Pathology Grand Rounds, University of Western Ontario. "Bilirubin Toxicity, Adverse Drug Effects and the Disulphide Proteome", February 8, 2006.

Bend, J.R.: Reactive oxygen species and the disulphide proteome. Invited speaker at a symposium titled "Proteomic approaches to studies of neuron function in health and disease", held at the Asia Pacific Regional Meeting of Neuro-Psychopharmacology: Challenging for Better Health, Pattaya, Thailand, March 14-17, 2006.

Bend, J.R., Organizer and Speaker, international Symposium of Topics in Environmental Pathology-Ecosystem Health, University of Western Ontario, London, Canada, October 18, 2006. Topic was Methylmercury as an ecosystem health concern to fish eating First Nation communities on the Canadian Great Lakes.

RECENT ABSTRACTS (since 1990)

Falkner. K.C., Cherian, M.G. and Bend, J.R.: Tissue specific effects of sodium arsenite on the cytochrome P-450 monooxygenase system. The Toxicologist 11:123, 1991.

Knickle, L.C., Woodcroft, K.J., Webb, C.D. and Bend, J.R.: 1-Aminobenzotriazole as an in vivo mechanism-based inhibitor of the cytochrome P-450 monooxygenase system of guinea pig liver, lung and kidney. The FASEB Journal 5: A479, 1991.

Knickle, L.C., Webb, C.D. and Bend, J.R.: Cytochrome P-450-dependent metabolism of arachidonic acid in guinea pig lung: effects of isozyme selective inhibitors. Can. Fed. Biol. Soc., Abstract 204, p.83, 1991.
Moffat, M.P., Bend, J.R., Farhangkhoee, P. and Karmazyn, M.: Actions of cytochrome P450-derived epoxides of arachidonic acid on normal and ischemic reperfused guinea pig hearts. J. Mol. Cell. Cardiol., 23: Suppl.3, S46, 1991.

McCallum, G.P., Falkner, K.C. and Bend, J.R.: Effects of sodium arsenite treatment on NAD(P)H:quinone oxidoreductase activity in lung, liver and kidney of rats and guinea pigs. Society of Toxicology of Canada Annual Meeting, Montreal, Dec., 1991.

Knickle, L.C., Webb, C.D. and Bend, J.R.: Cytochrome P450-dependent metabolism of arachidonic acid in guinea pig liver: effect of isozyme selective inhibitors. Toxicologist 12: 329, 1992.

Knickle, L.C. and Bend, J.R.: *N*-Aralkylated derivatives of 1-aminobenzotriazole are potent isozyme- and lung-selective inhibitors of guinea pig cytochrome P450 *in vivo*. The FASEB J. 6: A1569, 1992.

Woodcroft, K.J. and Bend, J.R.: Covalent binding of [^{14}C]1-aminobenzotriazole-derived radioactivity to guinea pig hepatic and pulmonary microsomal protein *in vitro*. The FASEB J. 6: A1566, 1992.

Bend, J.R., Knickle, L.C., Webb, C.D. and Woodcroft, K.J.: Isozyme selective mechanism-based inhibitors of pulmonary cytochrome P450 (Symposium). Toxicologist 13: 15, 1993.

Knickle, L.C., Webb, C.D. and Bend, J.R.: The guinea pig orthologue of cytochrome P450 2B4 is primarily responsible for the bioactivation of arachidonic acid to epoxyeicosatrienoic acids (EETs) in guinea pig lung. Toxicologist 13: 65, 1993.

Woodcroft, K.J., Knickle, L.C. and Bend, J.R.: *In vitro* and *in vivo* biotransformation and covalent binding to protein of two radiolabelled forms of the mechanism-based inhibitor, N-benzyl-1-aminobenzotriazole (^{14}C-phenyl or ^{14}C-benzyl) in guinea pig. Toxicologist 13: 65, 1993.

McCallum, G.P., Falkner, K.C. and Bend, J.R.: Cytochrome P450-1A1-dependent monooxygenase activity in guinea pig heart: Induction, inhibition and potentiation by exogenous NADPH-cytochrome P450 reductase. Can. Fed. Biol. Soc., Abstract 037, p.53, 1993.

Grimm, S.W., Philpot, R.M., Bend, J.R. and Halpert, J.R.: Differential hepatic expression, substrate specificity, and mechanism-based inactivation of rabbit cytochromes P450 2B4 and 2B5. Abstract, International Society for the Study of Xenobiotics Meeting, Arizona, 1993.

Sinal, C.J. and Bend, J.R.: Isozyme selective metabolic intermediate complexation of guinea pig hepatic cytochrome P450 by N-aralkylated derivatives of 1-aminobenzotriazole. Toxicologist 14: 50, 1994.

McCallum, G.P. and Bend, J.R.: Microsomal cytochrome P450 peroxygenase metabolism of arachidonic acid in guinea pig liver. Toxicologist 14: 51, 1994.

Rau, S.E., Bailey, D.B., Tran, L.T., Spence, J.D.and Bend,J.R.: Inhibition of terfenadine metabolism by co-administration of grapefruit juice in humans. Proceedings, 10th International Symposium on Microsomes and Drug Oxidations, p. 310, 1994.

McCallum, G.P. and Bend, J.R.: Alkylhydroperoxide-dependent oxidation of arachidonic acid in guinea pig pulmonary, cardiac and hepatic microsomes. Proceedings, 10th International Symposium on Microsomes and Drug Oxidations, p. 523, 1994.

Sinal, C.J. and Bend, J.R.: Inactivation rate constants for the mechanism-based inhibition of guinea pig hepatic and pulmonary cytochrome P450 2B and 1A isozymes by N-benzyl-1-aminobenzotriazole and N-α-methylbenzyl-1-aminobenzotriazole. Proceedings, 10th International Symposium on Microsomes and Drug Oxidations, p. 561, 1994.

Rau, S.E., Bend, J.R., Tran, L.T., Arnold, J.M.O., Spence, J.D. and Bailey, D.G.: Inhibition of terfenadine metabolism by co-administration of grapefruit juice in humans. Can. Assoc. Clin. Pharmacol. 1995.

Sinal, C.J., Zhu, L-F., Zhong, R., Cherian, M.G. and Bend, J.R.: Depression of multiple cytochrome P450-dependent monooxygenase activities after orthotopic liver transplantation in the rat. International Toxicologist, 35-P-31, 1995.

McCallum, G.P, Moffat, M.P., Karmazyn, M. and Bend, J.R.: Induction of P450 1A1 appwars to alter the cardiac response to arachidonic acid. International Toxicologist, 56-P-1, 1995.

Sinal, C.J., Albores, A., Falkner, K.C., Zhu, L.-F., Zhong, R., Cherian, M.G. and Bend, J.R.: Selective increase of rat pulmonary cytochrome P450 1A1-dependent monooxygenase activity during oxidant and/or pathobiological stress. Western Pharmacology Society, 38th Annual Meeting, January 22-27, 1995.

Kent, U.E., Bend, J.R. and Hollenberg, P.F.: Mechanism-based inactivation of cytochrome P450 2B1 by *N*-benzyl-1-aminobenzotriazole. Midwest Cytochrome P450 Symposium, Sept. 14-15, 1995.

Sinal, C.J., Webb, C.D., Vincent, R., Bouthillier, L. and Bend, J.R.: Modulation of rat hepatic and pulmonary cytochrome P450 after intratracheal administration of ambient air particulate matter. 37th Annual Meeting, Can. Fed. Biol. Soc., London, 1996.

Sinal, C.J. and Bend, J.R.: Modulation of liver, lung and kidney cytochrome P450 after acute sodium arsenite administration in the rat. 11th International Symposium on Microsomes and Drug Oxidations, Los Angeles, July, 1996.

Bailey, D.G., Rau, S.E., Munoz, C., Ito, S., Tesoro,A., Freeman, D.J., Spence, J.D. and Bend, J.R.: Inhibition of CYP3A and CYP1 iszymes by grapefruit juice and grapefruit juice constituents *in vivo* and *in vitro*. VIth World Congress on Clinical Pharmacology and Therapeutics, Buenos Aires, August 4-10, 1996.

Munoz, C., Ito, S., Bend, J.R., Tesoro, A>, Freeman, D, Spence, J.D. and Bailey, D.G.: Propafenone interaction with CYP3A4 inhibitors. Am. Soc. Clin. Pharmacol. Ther., Abstract PI-69, 61:154, 1997.

Sinal, C.J. and Bend, J.R.: Regulation of cytochrome P450 1A1 (CYP1A1) by heme and its endogenous metabolites. Am. Soc. Pharmacol. Exp. Ther., San Diego, March, 1997.

Yao, M., McCallum, G.P., Webb, C., Weedon, A.C. and Bend, J.R.: NADPH-dependent microsomal oxidation of the four regioisomeric epoxyeicosatrienoic acids by the renal cytochrome P450 monooxygenase system. Am. Soc. Pharmacol. Exp. Ther., San Diego, March, 1997.

Kent, U.M., Hanna, I.H., Szklarz, G.D., Vaz, A.D.N., Halpert, J.R., Bend, J.R. and Hollenberg, P.F.: Significance of glycine 478 in the metabolism of N-benzyl-1-aminobenzotriazole by cytochrome P450 2B1. 17th Int. Congress of Biochemistry and Molecular Biology and 1997 Annual Meeting, Am. Soc. Biochem. Mol. Biol., San Francisco, CA, August 1997.

Bailey, D.G., Kreeft, J.H., Freeman, D.J. and Bend, J.R.: Grapefruit juice-felodipine interaction: Amount and effect of active ingrediants in juice fractions in man. Am. Assoc. Clin. Pharmacol. Ther., 1998.

Seubert, J.M., Sinal, C.J. and Bend, J.R.: Modulation of Cytochrome P450 by arsenite in rat and CD57 BL/6 mice. Experimental Biology '99, Washington, DC, April, 1999.

Yaghi, A., Mehta, S., Bend, J.R. and McCormack, D.G.: Cytochrome P450 metabolites of arachidonic acid are depressed in lung homogenates of rats with acute *Pseudomonas* pneumonia. American Lung Association/American Thoracic Society International Conference, San Diego, CA, April, 1999.

Yaghi, A., Mehta, S., Bend, J.R. and McCormack, D.G.: Acute *Pseudomonas* in rats: role of arachidonic acid metabolites and nitric oxide. Winter Eicosanoid Conference, 1999. Baltimore, MD, March 7-10.

Bailey, D.G., Dresser, G.K., Kreeft, J.H., Munoz, C., Freeman, D.J. and Bend, J.R.: Grapefruit juice-felodipine interaction: effect of segments and an extract from unprocessed fruit. Am. Soc. Clin. Pharmacol. Ther., Los Angeles, CA, March, 2000.
Offman, E., Freeman, D.J., Dresser, G.K., Bend, J.R. and Bailey, D.G.: Cisapride interaction with grapefruit juice and red wine. Am. Soc. Clin. Pharmacol. Ther., Los Angeles, CA, March, 2000.

El-Kadi, A.O.S., Seubert, J.M., Castro, L.V., Webb, C.D., Yaremko, C.K. and Bend, J.R.: Effects of bilirubin and arsenite on glutathione S-transferase and NAD(P)H: quinoneoxido-reductase activities in mouse hepatoma HEPA 1C1C7 cells. Society of Toxicology, Philadelphia, PA, March 15-19, 2000.

Seubert, J.M., El-Kadi, A.O.S., Castro, L.V., Webb, C.D., Yaremko, C.K. and Bend, J.R.: Modulation of drug metabolizing enzymes following administration of bilirubin in rat. Society of Toxicology, Philadelphia, PA, March 15-19, 2000.

Yaremko, C.K., Webb, C.D. and Bend, J.R.: Isozyme-selective inactivation of hepatic microsomal cytochrome P450 by reactive oxygen species. Society of Toxicology, Philadelphia, PA, March 15-19, 2000.

Seubert, J.M., Darmon, A.J., El-Kadi, A.O., D'Souza, S.J. and Bend, J.R.: Bilirubin induces an apoptotic response in murine hepatoma cells. Society of Toxicology, San Francisco, CA, March, 2001.

El-Kadi, A.O., Seubert, J.M. and Bend, J.R.: Effect of inflammation alone or combined with bilirubin on aryl hydrocarbon receptor regulated genes in mouse hepatoma cells. Society of Toxicology, San Francisco, CA, March, 2001.

Yaghi, A., Weiker, S., Mehta, S., Bend, J.R. and McCormack, D.: iNOS inhibition restores the production of cytochrome P450 metabolites of arachidonic acid in lungs of rats with acute Pseudomonas pneumonia. Canadian Residents Competition in Respirology, Sept, 2001.

Bailey, D.G., Dresser, G.K. and Bend, J.R.: Lime-juice / red wine –felodipine interaction: comparison with grapefruit juice. Am. Soc. Clin. Pharmacol. Ther., Atlanta, GA, March, 2002.

Oakes, G.H., Seubert, J.M. and Bend, J.R.: Bilirubin induced ROS formation in mouse hepatoma (hepa 1c1c7) wild-type (WT aryl hydrocarbon receptor (AHR)-deficient (C12) and AHR nuclear translocator-deficient (C4) cell lines: Contribution to apoptosis. Society of Toxicology of Canada, Montreal, PQ, December, 2002.

Oakes G. H. and Bend J. R. 'Bilirubin Mediated Apoptosis is Characterized by the Production of Reactive Oxygen Species, Mitochondrial Membrane Depolarization and Caspase-3 Activation in Murine Hepatoma (Hepa 1c1c7) Cells..Poster presented at the M. Moffat Graduate Student Research Day, University of Western Ontario, May 11, 2004.

Bend, J.R., Oakes, G.H., Sarkissian, L. and Webb, C.D.: Bilirubin: a potential ligand of the aryl hydrocarbon receptor and an initiator of oxidative stress. 4th Scientific Meeting of the Oxidative Stress Consortium, Toronto, ON, May 21-23, 2004, pp.4.

Krizova, A., Tucker, J., Bend, J.R., Freeman, D., Dekaban, G. and Rieder, M.R.: Effect of HIV-1 Tat protein differential expression on cellular sensitivity to sulphamethoxazole hydroxylamine. 4th Scientific Meeting of the Oxidative Stress Consortium, Toronto, ON, May 21-23, 2004, pp.38.

Oakes, G.H. and Bend, J.R.: Bilirubin medoated apoptosis is characterized by the production of reactive oxygen species, mitochondrial membrane depolarization and initial caspase-9 activation in murine hepatoma (Hepa 1c1c7) cells. 4th Scientific Meeting of the Oxidative Stress Consortium, Toronto, ON, May 21-23, 2004, pp.45.

Oakes G. H., Sarkission L. and Bend J. R. 'Bilirubin Mediated Apoptosis is Characterized by the Production of Reactive Oxygen Species, Mitochondrial Membrane Depolarization and Caspase-3 Activation in Murine Hepatoma (Hepa 1c1c7) Cells.' Oral presentation at the Department of Paediatrics Research Day, University of Western Ontario, May 28, 2004.

Bend J. R., Oakes G. H., Seubert J. M., El-Kadi A. O., Castro Maya L. V. and Sinal C. J. 'Unconjugated bilirubin (UCB) as a prooxidant and potential ligand of the aryl hydrocarbon receptor (AhR). Trieste International Bilirubin Workshop 2004, Trieste Italy, October 1-2, 2004.

Yaghi, A., Bend, J.R., Zeldin, D.C., Mehta, S. and McCormack, D.G.: Mechanisms of depressed pulmonary artery contractility in a rat model of acute *Pseudomonas* pneumonia. Invited oral presentation: Merck Frosst Pharmacology Research Day, Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec (October 22, 2004).

Oakes, G.H and Bend J. R. 'Characterizing the molecular events leading to bilirubin mediated apoptosis: The role of aryl hydrocarbon receptor signalling.' Poster and oral presentation at the Canadian Society of Clinical Pharmacology (CSCP) Therapeutics Congress, Vancouver BC, April 15-19, 2005.

Albores, A., Xie, X., Dos Santos, J., Reid, C.R., Rieder, M.J. and Bend, J.R.: Non-enzymatic reaction of 2,4-dinitrochlorobenzene (DNCB) with Cys^{34} of human and bovine albumin: a model for covalent reaction of electrophilic metabolites causing adverse drug reactions (ADRs) at reactive cysteine thiol residues. Poster, Department of Paediatrics Research Day, University of Western Ontario, May, 2005.

Sarkissian, L. and Bend, J.R.: Modulation of intracellular redox status and unconjugated bilirubin (UCB)-mediated formation of reactive oxygen species (ROS) in hepatoma cell lines. Poster, Department of Paediatrics Research Day, University of Western Ontario, May, 2005.

Oakes, G.H. and Bend, J.R.: Unconjugated bilirubin causes oxidative stress In Murine hepatoma (Hepa 1c1c7) cells: Role of cytosolic glutathione In bilirubin toxicity. 38th Annual Meeting of the Society of Toxicology of Canada, Montreal, PQ, December, 5-6, 2005.

Sarkissian, L. and Bend, J.R.: Modulation of intracellular redox status and unconjugated bilirubin-mediated formation of reactive oxygen species in hepatoma cell lines. 38th Annual Meeting of the Society of Toxicology of Canada, Montreal, PQ, December, 5-6, 2005.

Xia, X., Albores, A., Dos Santos, J., Reid, C.R., Tucker, J., Rieder, M.R. and Bend, J.R.: Covalent reaction of electrophilic metabolites with CYS^{34} of human and bovine albumin: A method to monitor *in vivo* S-thiolation by drug metabolites implicated in adverse drug reactions. 38th Annual Meeting of the Society of Toxicology of Canada, Montreal, PQ, December, 5-6, 2005.

Oakes, G.H., Dale, L.B. and Bend, J.R.: Use of novel redox sensitive green fluorescent proteins to measure changes inintracellular redox status following treatment of cells with unconjugated bilirubin. Canadian Society of Clinical Pharmacology Therapeutics Congress, Toronto, ON, May 3-10, 2006.

Xia, X., Albores, A., Webb, C, Tucker, J, Rieder, M.J. and Bend, J.R.: The covalent binding of electrophilic metabolites with CYS^{34} of human and bovine albumin: a method to monitor S-thiolation by drug metabolites implicated in Adverse Drug Reactions (ADRs) *in vivo*. XVth World Congress of Pharmacology, Beijing, China, July 2-7, 2006.

Awaysheh, A., Oakes, G.H., Pitts, A. and Bend, J.R.: The effect of ROS-mediated oxidative stress in Hepa 1c1c7 cells on cellular proteins containing reactive protein cysteine thiol residues: Investigating the disulfide proteome Moffat Research Day, Schulich School of Medicine & Dentistry, March 22, 2007.

Oakes, G.H., Knauer, M.J. and Bend, J.R.: Nicotinic acid, an inhibitor of bilitranslocase, inhibits unconjugated bilirubin transport into murine Hepa1c1c7 cells. Moffat Research Day, Schulich School of Medicine & Dentistry, March 22, 2007.

Xia, X.Y., Schenke. M.E., Rylett, R.J. and Bend, J.R.: The protective effects of Baicalein on *t*-butylhydroperoxide-induced oxidative stress in HEK 293 cells overexpressing choline acetyltransferase. Moffat Research Day, Schulich School of Medicine & Dentistry, March 22, 2007.

Yip, C.S., Tucker, M.J., Bend, J.R. and Rieder, M.J.: The effect of common antioxidants found in Traditional Chinese Medicine on Sulfamethoxazole-induced toxicity. Moffat Research Day, Schulich School of Medicine & Dentistry, March 22, 2007.

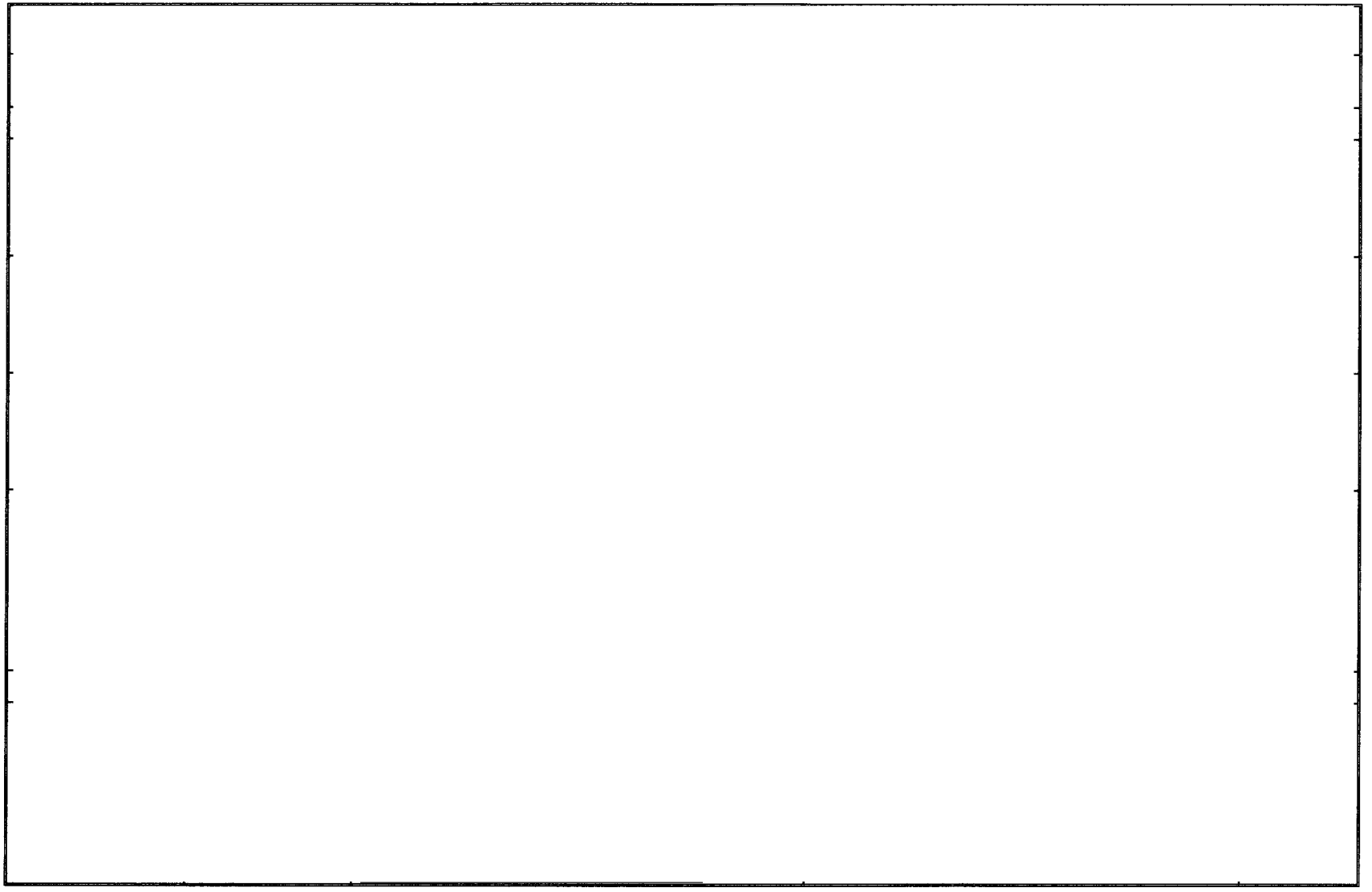
Oakes, G.H., Ayaysheh, A., Dale, L.B. and Bend, J.R. Unconjugated bilirubin causes changes in intracellular redox status, detected by novel redox sensitive green fluorescent proteins. 11th International Congress of Toxicology, Montreal, PQ, July 15 - 19, 2007.

Xia, X.Y., Rylett, R.J. and Bend, J.R. The protective effects of Baicalein on *t*-butyl hydroperoxide-induced oxidative stress in HEK 293 cells overexpressing choline acetyltransferase. 11th International Congress of Toxicology, Montreal. PQ, July 15 - 19, 2007.

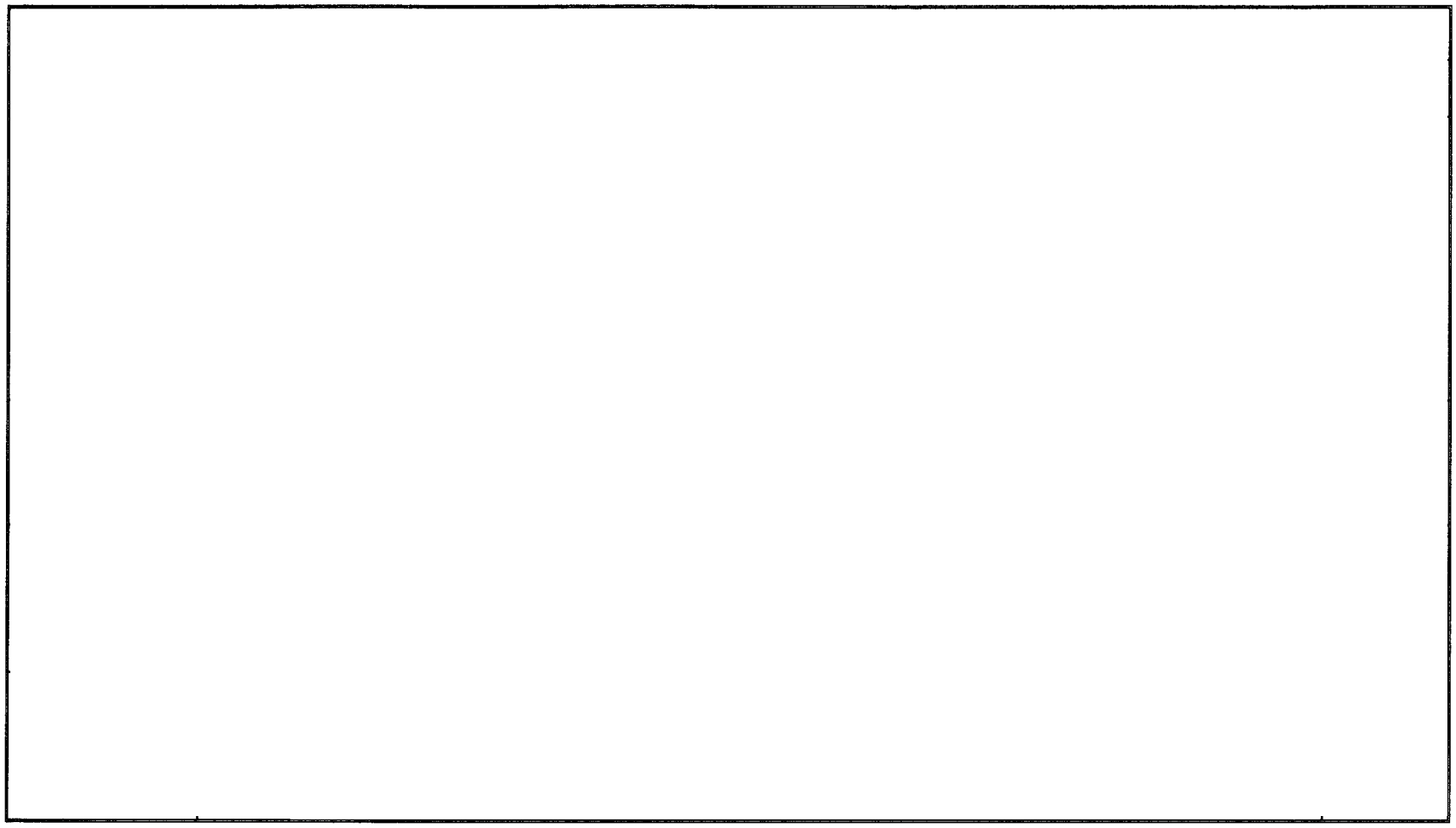
Attachment 2

Attachment 2

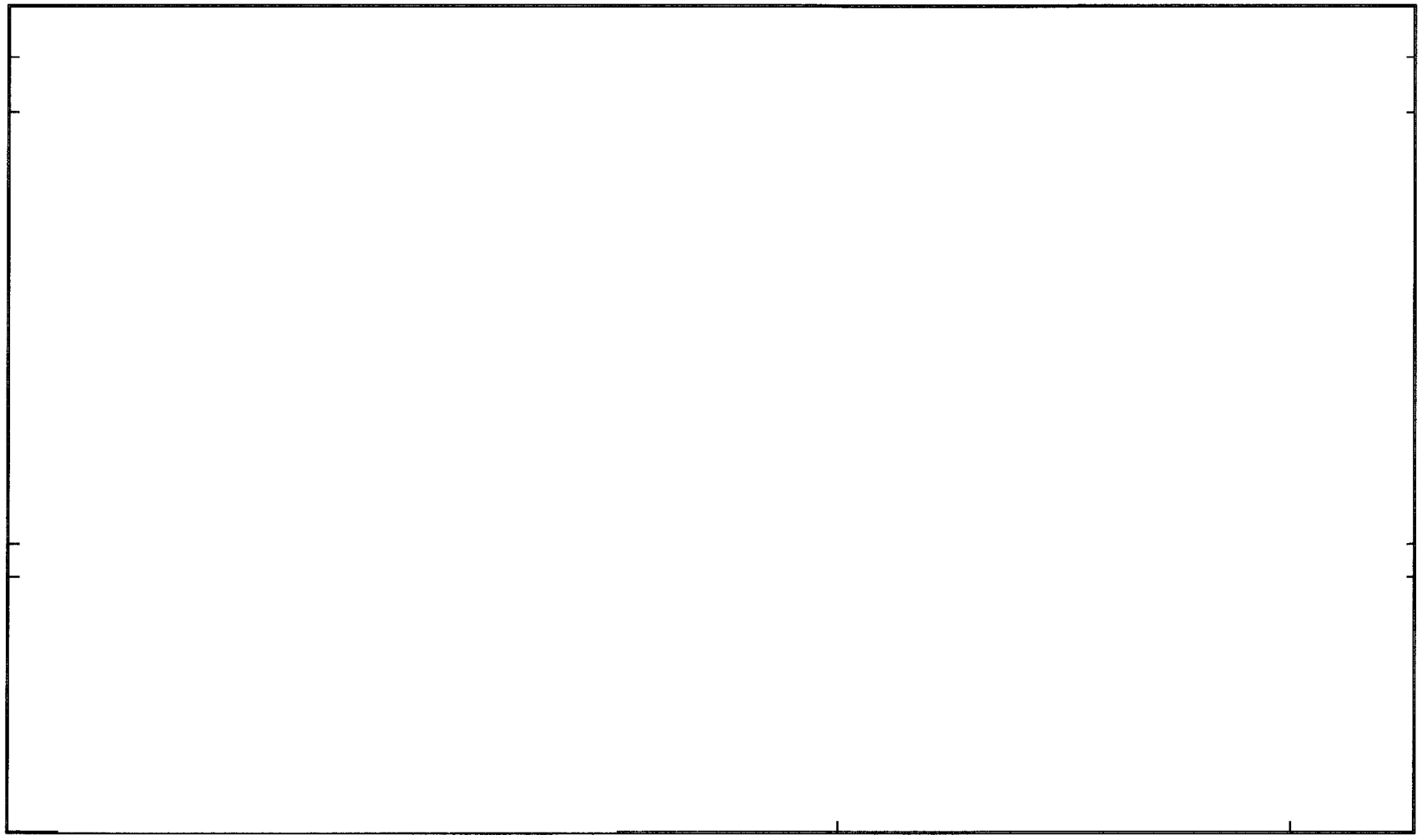
Summary of Toxicity Studies of GSH



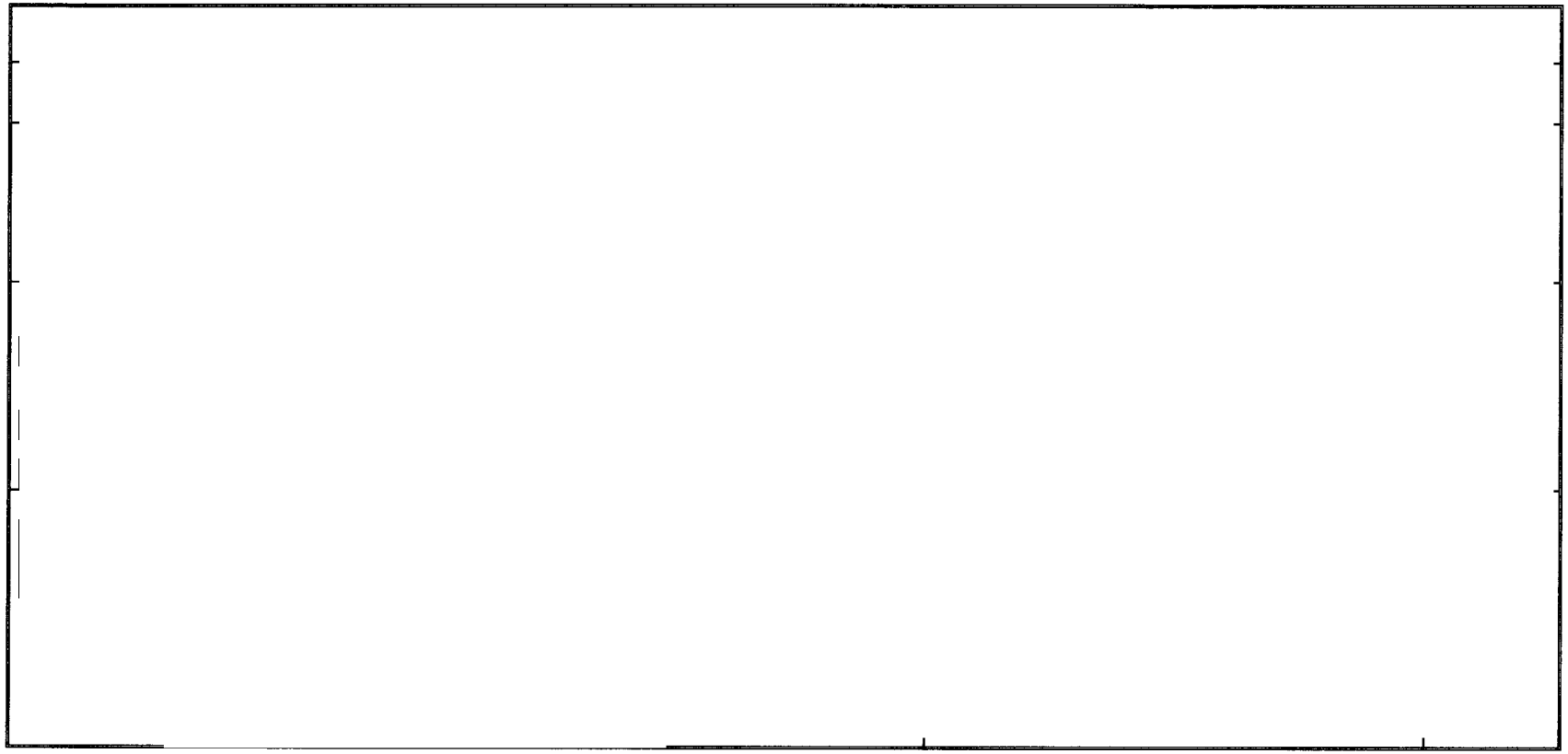
Summary of Toxicity Studies



Summary of Toxicity Studies



Summary of Toxicity Studies



	Reference

SUBMISSION END